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JOURNAL DE LA SOCIÉTÉ CANADIENNE DES ANESTHÉSISTES

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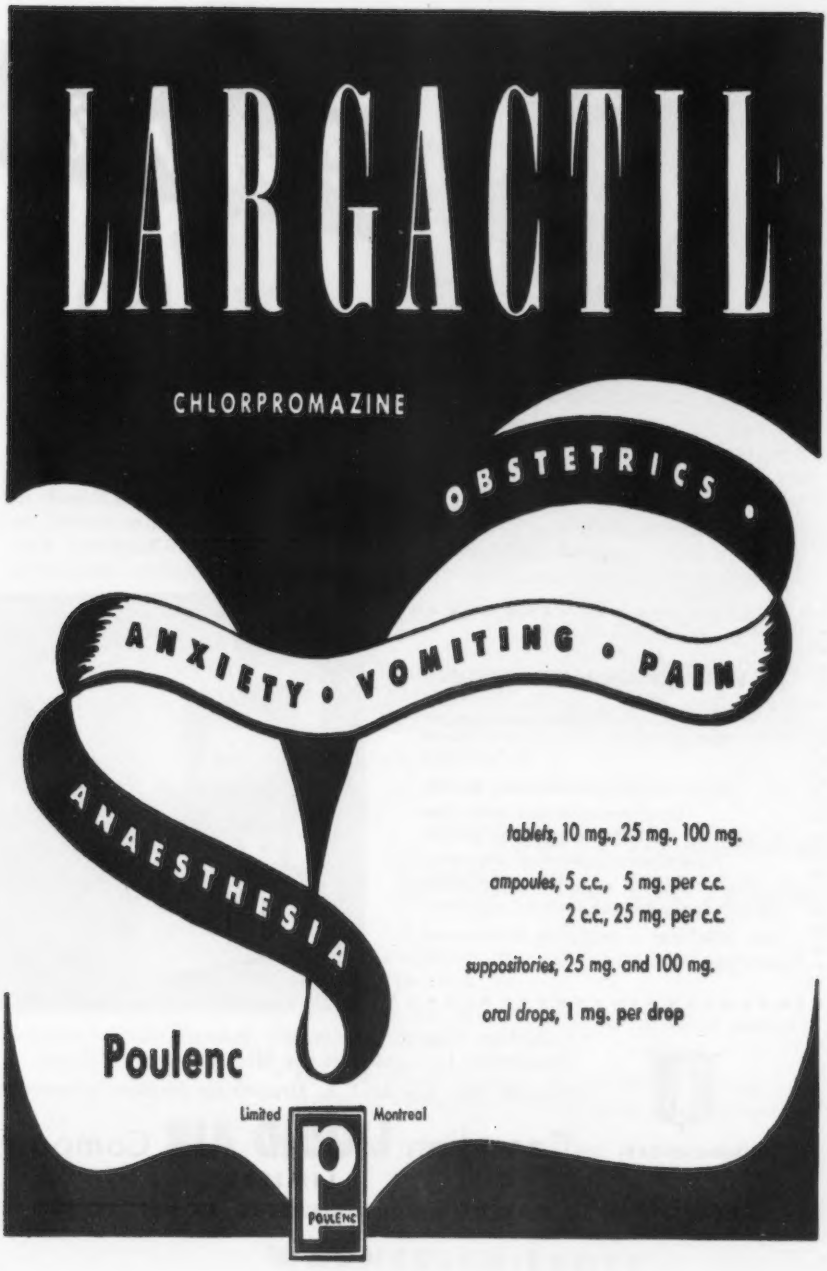
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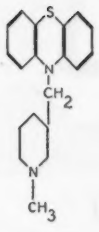

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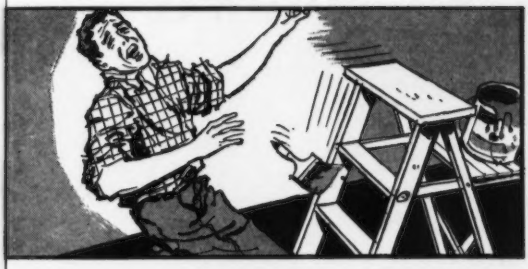

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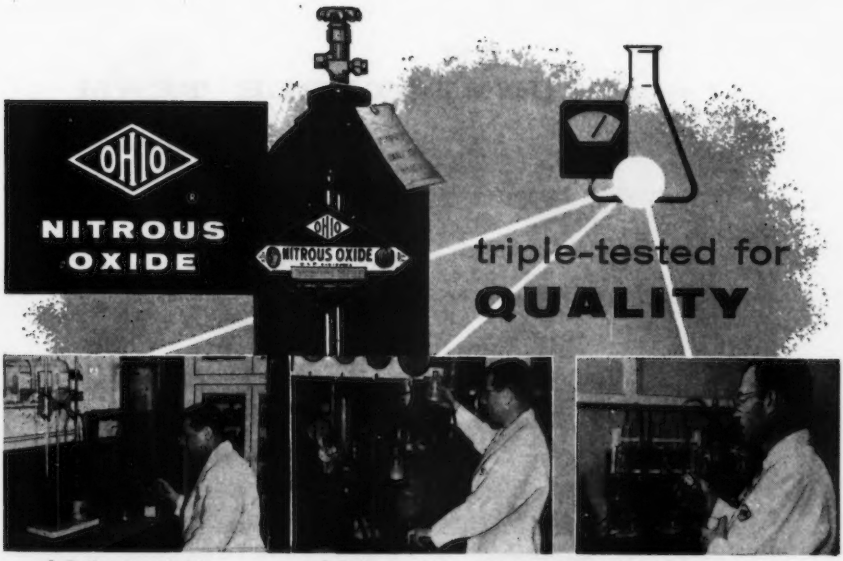

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1. Webster, C.W., C.M.A.J. Oct. 1953.

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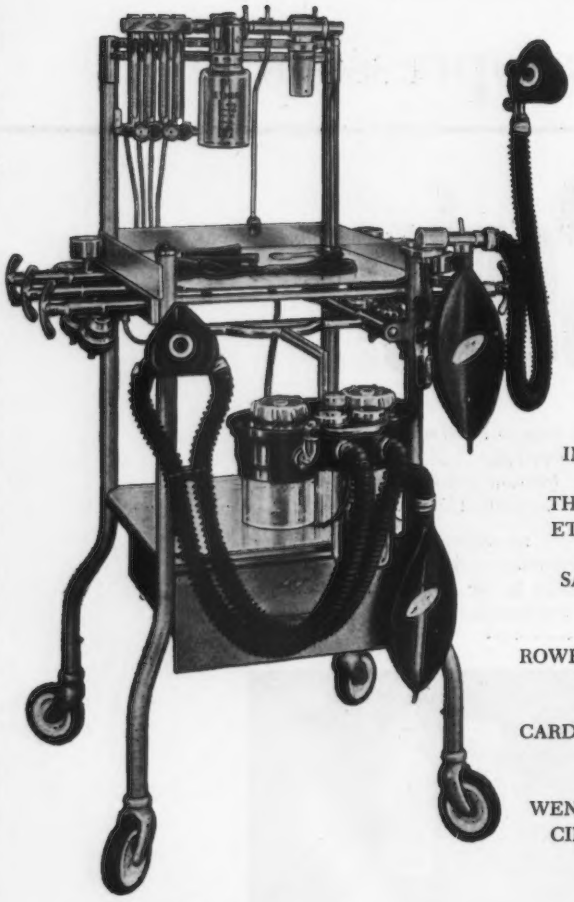

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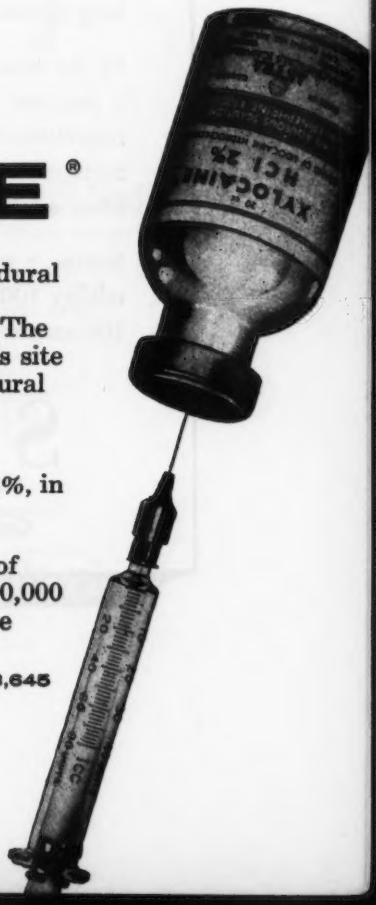

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EDITORIAL

The Teaching of Anaesthesia

One becomes increasingly aware that while much thought is given by clinical teachers of medicine generally to the problem of *what* to teach students at all levels of training, much too little thought is given to *how* to teach them. This general observation applies as well to teachers of anaesthesia as to those in other branches of the profession of medicine.

Our modern undergraduate curriculum has become so crowded that no teacher in a medical school today could pretend to convey to his students a detailed knowledge of his particular branch of medical practice. If a detailed and particular knowledge is impracticable, what type of training, then, should the undergraduate receive?

It would appear that the greatest service which the teacher in a special field of medicine could provide to a student would be to assist him to appreciate the problems related to that special field in terms of the physiology, pharmacology, biochemistry and anatomy which he already knows (or should know), and to relate these special problems in a logical way to the knowledge of general medicine which he is presently acquiring, and which should also be built systematically on his knowledge of the basic sciences. In his contacts with the undergraduate the teacher must emphasize the "*what*" and the "*why*" of his subject, and, so far as possible, train his student by the process of reasoning to arrive at the "*how*" of any situation. "*Know-how*" may be admirable in a technician, but a physician can only be competent when he also has "*know-why.*"

The methods of training of the post-graduate student in the specialty require still further consideration. The older generation of anaesthetists who are now gradually retiring from the scene have grown with the specialty, and have brought us from the *rag-and-bottle* and *whiff-of-gas* era to the complexities of modern anaesthesia through decades of progress, when their long experience and developed judgment led them easily from one step to the next. The problem of the teacher of the fledgling anaesthetist today is to conduct his young charge through this same progress in the space of two or three years. This process can only be successful if again, "*what?*" and "*why?*" are the dominant themes in the teaching, the problems of "*how?*" standing not alone as technical feats but as logical answers derived from the other factors through reason.

There have been widely divergent views of the best method of achieving this logical organization of our teaching. Some teachers would consider clinical anaesthesia purely as applied pharmacology, and the application in the operating room of the methods learned in and transferred from the laboratory as the logical and adequate solution. We are aware that this programme in practice has produced many admirable scientists who are poor clinical anaesthetists. Conversely, we are aware of many excellent clinical anaesthetists who are so because of superior intuition and practised judgment, and who are unable to explain their activities in sound or logical terms.

Surely the best we can do for the developing anaesthetist is to give him the

best of these apposite types. He must be offered a firm foundation in basic medical science, and wide experience in the operating room. He must, moreover, be required in his clinical work to explain and justify himself at every step. Only in this way can he hope to achieve in his few years of training the standard developed by his predecessors through many decades. Only in assuring such a training does his teacher adequately fill his role.

On the Introduction of a New Drug: Fluothane

We have previously in this Journal discussed the principal requirements for the evaluation of new drugs in anaesthesia (1) and the philosophy of the investigation and reporting of clinical trials of new drugs (2). In this issue we are privileged to present at one time reports of several different and independent investigations of the clinical use of a new volatile anaesthetic agent, Fluothane.

It appears evident that Fluothane combines desirous and admirable properties with potentially dangerous activity which may produce fatalities in the hands of the unwary. While such a combination of properties is not new to the trained anaesthetist, there has in the past been a regrettable tendency for some enthusiasts to embark on the wholesale use of a new drug or a new method, without due regard to the aspects of safety. When this occurs the tragic results of poor judgment are too often attributed to the drug or the method, in general terms.

We hope sincerely that the simultaneous presentation to our readers of diverse reports on the clinical use of *Fluothane* will help to provide the basis of a rational and careful introduction of this drug to clinical practice.

REFERENCES

1. Melville, K. J. Editorial: Evaluation of New Drugs in Anaesthesia. Canad. Anaesth. Soc. J., 2: 1 (1955).
2. Editorial: New Drugs. Canad. Anaesth. Soc. J., 3: 289 (1956).

EDITORIAL

L'Enseignement de l'anesthésiologie

On peut se rendre compte de plus en plus que les professeurs de clinique médicale, de façon générale, s'attardent davantage sur le problème de savoir *quoi* enseigner aux différents niveaux de l'entraînement que sur le problème de savoir *comment* enseigner. Cette remarque générale concerne aussi bien les professeurs d'anesthésiologie que ceux des autres spécialités de la profession médicale.

Notre programme universitaire moderne est devenu tellement chargé qu'aucun professeur d'une école de médecine ne peut prétendre, aujourd'hui, servir à ses élèves les connaissances détaillées de sa spécialité dans la pratique médicale.

S'il est impossible de fournir des connaissances particulières détaillées, quelle sorte d'entraînement, alors, doit recevoir l'étudiant en médecine?

Il semblerait que le plus grand service que le professeur d'une spécialité médicale peut rendre à un élève serait d'aider cet élève à étudier les problèmes de cette spécialité en rapport avec la physiologie, la pharmacologie, la biochimie et l'anatomie qu'il sait déjà (ou qu'il devrait savoir) et de faire la relation, de façon logique, de ces problèmes spéciaux avec les connaissances de la médecine générale, connaissances qu'il est en train d'acquérir et qui, elles-mêmes, systématiquement, devraient être basées sur ses connaissances des sciences de base. Au cours de ses entretiens avec l'élève, le professeur doit insister sur le "quoi" et le "pourquoi" du sujet et, autant que possible, habituer l'élève à raisonner pour en venir au "comment" en toute circonstance. "*Savoir comment*" peut être très précieux pour un technicien, mais pour qu'un médecin soit compétent, il faut qu'il sache également "*pourquoi.*"

Les façons d'enseigner aux élèves du cours post-universitaire d'une spécialité demandent encore plus d'attention. La génération des anesthésistes plus âgés qui commencent actuellement à se retirer de la scène mais qui ont grandi dans le spécialité nous ont transportés de l'ère de la *compresse et de la bouteille* et de la *bouffée de gaz* aux problèmes complexes de l'anesthésie moderne en suivant des décades de progrès alors que leur longue expérience et leur souple jugement leur ont permis de passer facilement d'un pas à l'autre. Aujourd'hui, le problème du professeur envers le futur anesthésiste est de lui faire parcourir la même route en deux ou trois ans. Cette façon de faire ne peut conduire au succès qu'à la condition que les "quoi" et les "pourquoi" demeurent les thèmes dominants de l'enseignement, que les problèmes du "comment" ne demeurent pas seulement des tours de force de la technique, mais des réponses logiques découlant des autres facteurs par l'intermédiaire de la raison.

Il a existé de grandes divergences d'opinion au sujet de la meilleure méthode de réaliser cette organisation logique de l'enseignement. Certains professeurs auraient tendance à considérer l'anesthésie clinique uniquement comme de la pharmacologie appliquée et l'implantation des méthodes apprises au laboratoire et apportées à la salle d'opération comme une solution logique et adéquate. En pratique, nous réalisons que ce programme a produit plusieurs hommes de

science distingués mais de piètres anesthésistes cliniques. Par contre, nous connaissons de nombreux anesthésistes cliniques de première qualité dont les capacités sont dues à une intuition supérieure et à un jugement pratique mais qui sont incapables d'expliquer leurs décisions en des termes précis et logiques.

Sans doute, le mieux à faire pour l'anesthésiste en formation, c'est de lui donner la meilleure part de ces deux types opposés. On doit lui faire acquérir une formation solide dans les sciences de base médicale et une grande expérience dans la salle d'opération. De plus, on doit exiger de lui, au cours de son travail clinique, l'explication et la justification de tous ses gestes. C'est de cette façon seulement que l'on peut espérer réaliser, chez eux, en quelques années d'entraînement le niveau atteint par leurs prédécesseurs au cours de plusieurs décades. Puis, c'est seulement en réalisant un entraînement de cette qualité que leur professeur remplit adéquatement son rôle.

Au sujet de l'admission d'un nouveau médicament: Fluothane

Antérieurement, dans ce même Journal, nous avons énuméré les principaux facteurs à étudier pour évaluer des médicaments nouveaux en anesthésie (1) et exposé la philosophie qui doit présider à la recherche et au reportage des épreuves cliniques de ces nouveaux médicaments (2). Dans ce numéro-ci, nous sommes heureux de présenter en même temps les résultats de plusieurs recherches différentes et indépendantes sur l'usage clinique d'un nouvel agent anesthésique volatile, Fluothane.

Il semble manifeste que le Fluothane associe de précieuses et désirables qualités à une activité éventuellement dangereuse pouvant entraîner des morts dans les mains de celui qui n'est pas averti. Bien que l'association de semblables propriétées ne soit pas nouvelle pour l'anesthésiste expérimenté, on a constaté, dans le passé, chez certains enthousiastes, une regrettable tendance à employer à tout hasard un nouveau médicament ou une nouvelle méthode, sans considérer le point de vue de sécurité. Dans cette occurrence, les résultats tragiques du manque de jugement retombent souvent, de façon générale, sur le médicament ou la méthode.

Nous avons une ferme confiance que la présentation simultanée, à nos lecteurs, de plusieurs résultats sur l'emploi clinique du Fluothane contribuera à établir une base pour l'admission progressive et prudente de ce nouveau médicament dans la pratique clinique.

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CLINICAL EXPERIENCE WITH FLUOTHANE®, A NEW NON-EXPLOSIVE ANAESTHETIC AGENT*

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FOR MANY YEARS anaesthetists have felt the need for a non-explosive anaesthetic agent possessing none of the disadvantages associated with chloroform, trichlorethylene and nitrous oxide. That is, the agent should be non-hepatotoxic, stable in the presence of soda lime and heat, and have a high therapeutic ratio.

Since most heavily fluorinated hydrocarbons are not inflammable, and many possess anaesthetic properties, they present interesting possibilities. Robbins (1) found that some hydrocarbons had greater therapeutic ratios than chloroform or ether, but that when they were used, severe hypotension, cardiac arrhythmias and stimulation of skeletal muscle occurred.

In 1956, Raventós and Suckling synthesized and investigated a series of fluorinated hydrocarbons, and one in particular–CF_3 CHClBr (Fluothane)–was found to have potent anaesthetic properties (2). The first clinical trial has been reported by Johnstone (3) who studied the human cardiovascular response to Fluothane®.

PHYSICAL PROPERTIES

Fluothane® is a clear colourless liquid with a rather pleasant odour. It has a specific gravity of 1.86 at 20° C. and a boiling point of 50.2° C. Vapour pressure at 20° C. is 243 mm. Hg. Oil/water solubility is 330 compared to 100 for chloroform and 3.2 for ether. When exposed to light, Fluothane decomposes slowly, forming volatile acids. This can be prevented by storing it in amber-coloured bottles or by adding thymol 0.01 per cent W/W. Fluothane is non-inflammable, non-explosive and stable in the presence of soda lime.

Fluothane should not be confused with Fluomar® (trifluoro-ethyl-vinyl ether), an inflammable fluorinated ether with somewhat different properties, described by Orth (4) and Gainza, *et al.* (5).

PHARMACOLOGY

Raventós (2) investigated the pharmacological actions of Fluothane in animals and reported that full surgical anaesthesia was achieved after using a 2–4 per cent concentration of Fluothane in air or oxygen for two to five minutes.

Anaesthesia was maintained with a concentration of 0.4–0.8 per cent in premedicated dogs, and 1–1.2 per cent in unpremedicated ones. On the basis of

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these findings Fluothane would seem to have double the potency of chloroform and four times that of ether.

Respiration was decreased in amplitude and rate, but especially in rate. When administration was continued to respiratory arrest, blood pressure was still 60–80 mm. Hg, and the heart continued to beat for nine to ten minutes.

Blood pressure fell in proportion to the vapour concentration and the fall was most marked during induction.

Heart rate was consistently slowed, but no irregularities were noted except in the presence of epinephrine and norepinephrine, when ventricular tachycardia and ventricular fibrillation were produced.

Salivation and mucous secretions were abolished, and vomiting did not occur at any time. No significant functional or histological changes were found in liver or kidneys in animals, after prolonged Fluothane anaesthesia.

In view of the interesting properties of Fluothane, it was felt that a trial should be made with a wide variety of cases to assess its suitability for clinical use.

The series was divided into two parts—Series I and II. In Series I, Fluothane was used in a closed circuit soda lime absorption system, for the most part using Fluothane for induction also (H.H.M.). In Series II, Fluothane was used in the semi-closed system, following thiopentone induction (J.C.).

SERIES I: USE OF FLUOTHANE IN THE CLOSED CIRCUIT

Selection of Cases

The series consisted of 120 consecutive cases assigned to the particular operating room in which the author was working. Only young children were excluded as it was felt that the use of an experimental agent with a closed circuit in these cases was potentially hazardous.

Age of Patients

Ages ranged from 17–84 years, with approximately an even number in each decade between 20 and 80.

Types of Surgical Procedures

Duration of surgery ranged from 15 minutes to 4½ hours with the majority of the cases lasting 2 hours and under.

Anaesthetic Equipment

The ether vaporizers on the Foregger, Heidbrink, McKesson and Chicago Anaesthetic machines were used, concentration of Fluothane being judged on purely clinical observations.

Those vaporizers employing a wick appeared to be the most satisfactory.

METHOD

Premedication. This was standardized as far as possible with the average male receiving a short-acting oral barbiturate, gr. 1½, two hours preoperatively,

followed by morphine, gr. ¼, and hyoscine, gr. 1/100, one hour preoperatively. These dosages were reduced for small females, the severely ill and the aged.

In 33 cases intravenous atropine gr. 1/200–1/50 was given 10 minutes prior to induction. The effect of this will be discussed below.

Prior to induction, blood pressure, respiratory and pulse rate were recorded. In 21 cases simultaneous respiratory rate, minute and tidal volumes were measured, using a Monaghan ventilation meter.

Type	*Number*	*Type*	*Number*
General surgery		Plastic surgery	6
Major	23	Orthopaedic surgery	
Minor	15	Major	4
Gynaecological surgery		Minor	1
Major	14	Thoracic surgery	4
Minor	19	Genito-urinary surgery	
Abdominal surgery	21	Major	2
Vascular surgery	10	Minor	1

Induction. Intravenous thiopentone was used to induce 24 patients, while the remaining 96 were induced with Fluothane by mask. The technique was as follows:

The patient was first asked to breathe a mixture of N_2O and O_2, 4 and 2 litres per minute respectively. When the patient was lightly asleep, Fluothane was gradually turned into the circuit and the N_2O turned off. (Although Fluothane/O_2 induction was not unpleasant, preliminary N_2O induction proved to be more agreeable to the majority of patients.)

After about 10 minutes of Fluothane, the vaporizer setting had generally reached the three-quarter mark and blood pressure had fallen to about 60 mm. Hg. By this time sufficient anaesthesia was usually present for surgery; so the O_2 was turned down to basal requirements and the circuit closed. Fluothane now was either turned off or turned back to the lowest setting. About 10 minutes prior to completion of surgery, the Fluothane was turned off completely and a 4/2 litre per minute flow of N_2O/O_2 started, in order to eliminate as much Fluothane as possible.

During the procedure blood pressure, pulse and respiration rates were recorded at 5-minute intervals, as well as frequent minute and tidal respiratory volumes for 21 patients.

Where indicated, intubation was performed following a relaxant, the other patients being carried with a mask.

Results

With adequate premedication, Fluothane induction was moderately rapid and smooth, free from coughing, laryngospasm, or salivation. With light premedication, induction tended to be slower and was often marked by violent struggling with a period of generalized muscle rigidity. During this period masseter spasm often prevented insertion of an oral airway.

After ten minutes the muscle rigidity gave way to relaxation and after fifteen minutes, surgery could be commenced, although reflex movement was occasionally observed. This was associated with a rise in blood pressure and tachypnoea.

After 20–25 minutes, reflex movement was abolished, though abdominal relaxation was insufficient for upper abdominal exploration. At this time intubation

could be performed without the need for a relaxant, the cords, being widely abducted.

Cardiovascular System

Effect on Blood Pressure (Table I)

Within the first few minutes of Fluothane induction, pulse rate and blood pressure declined progressively, systolic fall being relatively greater than diastolic, resulting in a low pulse pressure. Fall in blood pressure appeared to be directly related to the concentration of Fluothane and especially to the rapidity with which concentration was increased. The average fall in pressure during Fluothane induction (taken as the first 30-minute period) was 42 mm. Hg.

TABLE I

Degree of Hypotension during Induction

B.P. drop mm. Hg	Number of cases		
	Total series	Series without pre-induction I.V. atropine	Series with pre-induction I.V. atropine
Nil	6	4	2
–20	37	22	15
21–40	37	29	8
41–60	18	14	4
61–80	10	8	2
81–100	7	6	1
110–120	1	1	0
121–140	3	2	1
141–160	1	1	0
Total	120	87	33
Average B.P. drop mm. Hg	40	43	31

Average Fluothane® induction B.P. fall, 42 mm. Hg.
Average Pentothal/Fluothane® induction B.P. fall, 46 mm. Hg.

After the initial fall and when the vaporizer setting was decreased, blood pressure usually rose to around 80 mm. Hg and fluctuated on either side of this level, depending on the setting of the vaporizer.

Effect of Atropine on Induction Hypotension (Table I)

Atropine gr. 1/200–1/50 was given to 33 patients intravenously 10 minutes prior to induction, to see if preventing bradycardia could affect the fall in blood pressure. Within a few minutes of injection, blood pressure rose on the average 20 mm. Hg and pulse rate increased to about 120 per minute. Following induction, blood pressure declined as in the non-atropinized patients, though to a lesser extent.

The average fall in the atropinized patients was 31 mm. Hg. During maintenance, average blood pressures in these patients were about 10 mm. Hg higher than in non-atropinized patients. In fact, in many patients who were given

atropine, systolic blood pressure and pulse rate were frequently numerically equal, while in the non-atropinized ones pulse rate and diastolic blood pressure were often equal, or nearly so.

Effect of Age on Induction Hypotension

In the entire series there were 37 patients, 60 years of age or over. The average fall in blood pressure for them was 44 mm. Hg compared with 45 mm. Hg for the patients under 60 years of age.

In the eleven patients 60 years of age and over who were given intravenous atropine prior to induction, the average fall was only 27 mm. Hg, while the remaining 26 who received no atropine had an average fall of 51 mm. Hg.

Although the number of patients in each group is relatively small, it would appear that only in the older age groups was any significant benefit derived from pre-induction atropine.

Degree of Induction Hypotension

All degrees of hypotension were seen, from no perceptible decrease to complete absence of recordable blood pressure or pulse, the latter occurring in twelve patients (10 per cent). In Table II, the degree of hypotension sustained is shown. As can be seen, there is no very significant protection afforded by atropine in the over-all series.

Severe Hypotension Episodes

In the twelve patients referred to above, blood pressure and palpable radial and carotid pulsation disappeared following attempts to deepen the anaesthesia. It appeared as if cardiac standstill had occurred in each case, the only hopeful signs of continuing circulation being the fact that the skin remained pink and warm, and a faint capillary refill was present.

Except for one case which will be described in detail below, inflation of the lungs with 100 per cent oxygen rapidly restored blood pressure and pulse within a minute. This was found to be the most reliable treatment, as neither vasopressors nor atropine at this time were very effective, since circulation was sluggish. Less profound hypotension responded better to Methedrine® than to Neosynephrine®, the latter commonly causing frequent extrasystoles.

Since blood pressure returned so rapidly, it was felt that the sudden hypotension was mainly due to sudden increase in concentration of Fluothane, causing myocardial depression.

After analysing the twelve cases, it was seen that in every one concentration had been increased just prior to the episode, and except for two cases, followed manual ventilation after the use of a relaxant. Succinylcholine was the relaxant in seven, C_{10} in one, and gallamine in two cases.

Except for one instance, all episodes occurred within the first 30 minutes following induction. Of the twelve patients, five had intravenous atropine before induction, which conferred no protection against hypotension of this sort.

No relaxant was given to two patients prior to the hypotensive episode, but thiopentone in small doses was given in addition to increasing Fluothane® concentration.

Cardiac Arrest

One cardiac arrest occurred in the entire series, though fortunately without fatal result.

Case report. A 38-year-old white male was to undergo a transthoracic vagotomy for treatment of a chronic stomal ulcer. Preoperative examination showed an otherwise healthy 155-lb. man, B.P. 120/80, pulse 72/minute.

Premedication consisted of morphine gr. 1/6 and hyoscine 1/100 gr., given 1 hour preoperatively.

The patient was induced at 11:00 A.M. with thiopentone 500 mg. and intubated following decamethonium 3 mg. with a cuffed # 9 O.T. tube. He was maintained on Fluothane/O_2 in a closed circuit and was postured in the right lateral position with the table flexed.

Following the induction and positioning of the patient, blood pressure gradually declined as expected with Fluothane, and at 11:25 A.M., blood pressure was 80/60 mm. Hg and pulse 60/minute. Atropine gr. 1/100 was given intravenously in order to correct the hypotension.

As the surgeon made the skin incision the patient began to shiver violently and made movements as if reacting to the stimulus. As it appeared the patient was in a light plane of anaesthesia, thiopentone 125 mg. was given and the Fluothane vaporizer setting increased, ventilation all this time being controlled.

At 11:35 A.M., blood pressure and pulse, which had been carefully watched, suddenly disappeared and Methedrine® 20 mg. was given intravenously, together with inflation with 100 per cent O_2 with the Fluothane turned off.

The face now appeared slightly cyanosed and bleeding in the wound ceased. The surgeon was advised that a cardiac arrest was probable and the thoracotomy was rapidly completed.

On opening the chest cavity, the heart was seen to be in standstill but still pink, and immediate manual compression was performed. After 4 compressions the heart restarted, blood pressure could be just obtained at 45 mm. Hg, and the surgeon observed that the heart when first palpated was flabby. Suddenly ventricular fibrillation commenced and heart was compressed for a further minute, till the electrical defibrillator could be set up.

After 4 separate shocks of 220 v. at 0.2 sec., defibrillation was successful. Following a few seconds of asystole, the heart began to beat rapidly and irregularly, blood pressure rising to 180/140 mm. Hg, presumably in part owing to the Methedrine®. The pericardium was not opened.

The surgery was completed at 1:30 P.M. and by that time blood pressure was 120/80 mm. Hg and pulse 100/minute.

The patient was transferred to the recovery room, and by 1:45 P.M., was reacting, and at 2:00 P.M. was conscious. E.C.G. taken at this time was completely normal.

The patient made a speedy recovery from the surgery and showed no evidence whatsoever of cerebral damage. He was discharged after 10 days and resumed work shortly after.

It was estimated that circulation had been arrested for a period of 1 to 1½ minutes.

Blood Pressure during Maintenance

Using Fluothane in the closed circuit it was rarely possible to maintain a steady blood pressure level, as small changes in the vaporizer setting caused almost immediate alteration.

Degree of myocardial depression and depth of anaesthesia did not seem necessarily related, as blood pressure, especially in the induction period, could be quite low and yet there was reaction to surgical stimulus, as illustrated in the case described above where cardiac arrest occurred.

After several hours a smooth level appeared to be easier to maintain, possibly because of decreased blood/tissue gradients.

Effect on Pulse Rate and Rhythm

Rate. During induction pulse rate slowed with decline in blood pressure. In the majority of patients pulse fell to 60 per minute and remained about that level until anaethesia was lightened, when it rose to around 70 per minute. Rates as low as 40 per minute have been noted, and with the use of intravenous atropine may run from 80–120 per minute with similar systolic blood pressure.

Rhythm. Fluothane caused pulse irregularities in seventeen patients. These took the form of irregularly spaced extrasystoles, showing as occasional weak beats, and a peculiar bigeminal rhythm with a pulsus alternans character. These were diagnosed by palpation of the radial pulse and noted alteration in blood pressure level.

There appeared to be a zone of anaesthesia in which arrhythmias occurred, as deepening or lightening the anaesthesia, especially the latter, often caused the pulse to become regular.

Two cases, in which atropine was given intravenously, immediately converted to a faster regular rhythm. In five cases with bigeminal rhythm, atropine had been given intravenously just before induction, so did not appear to have had any prophylactic value.

No particular age group was immune or especially susceptible to arrythmias, these being seen in patients aged from 20–82 years.

Bleeding. This was greatly diminished, possibly owing to decreased pulse pressure and in part to a relative hypotension. However, bleeding was also minimal even where blood pressure was still close to the preoperative level. The diminution in bleeding was one of the most remarkable properties of Fluothane and affected all but the larger arterioles which still bled normally.

Postoperative haemorrhage of the wound occurred in two patients, but appeared to be due to a slipped ligature in each case.

Venous system. Early in induction the veins became very prominent and even tense, suggesting a raised venous pressure, possibly due to a decreased cardiac output.

Postoperative blood pressure. Blood pressure readings were taken immediately on the patient's return to the recovery room and show the following results:

Higher blood pressure than preoperative level, 27 per cent.
Same blood pressure as preoperatively, 22 per cent.
Blood pressure drop of not more than 20 mm. below preoperative level, 31 per cent.
Blood pressure 21–40 mm. Hg below preoperative level, most of which were readily corrected by elevating the foot of the bed, 10 per cent (2 cases responded promptly and permanently to Methedrine®).
Fall below 40 per cent, 0.
Immediate postoperative blood pressures not recorded, 10 per cent.

Respiratory System

In 21 cases minute volumes, tidal volumes and respiratory rates were correlated using a Monaghan Ventilation Meter. As can be seen from Table II, most patients had some degree of respiratory depression on arrival in the operating

suite due to preoperative sedation. Depression was proportionately greater in women than men.

TABLE II

PREOPERATIVE VENTILATION

Age	Weight (lb.)	Minute volume (litres)	Tidal volume (cc.)	Rate
MALES				
68	–	8.6	610	14
54	–	6.0	500	12
26	138	5.2	300	17
66	165	4.8	260	18
48	145	4.8	260	18
74	–	4.2	300	14
50	–	4.0	330	12
75	–	4.0	330	12
66	168	3.3	470	7
FEMALES				
43	160	8.0	500	16
41	–	6.0	500	12
37	181	4.0	220	18
60	–	3.6	360	10
37	130	3.2	320	10
66	–	3.0	165	18
25	–	2.6	160	16
46	118	2.6	260	10
65	160	2.2	200	11
50	120	2.0	100	20

As illustrated in Figures 1, 2 and 3, during induction there was a progressive increase in respiratory rate, associated first with a transient increase in tidal and minute volumes as unconsciousness occurred. This rapidly changed to faster and shallower breathing, causing a progressive decrease in tidal and minute volumes when anaesthesia became light. With surgical stimulus respiration became very fast—up to 40 per minute and was associated with larger tidal volumes, resulting in large minute volumes—up to 12 litres per minute.

When anaesthesia was deepened, respiratory rates usually increased and respirations became very shallow, with sharp decreases in tidal and minute volumes. Progressive deepening of anaesthesia finally led to complete apnoea, though blood pressure was still usually around 70 mm. Hg.

Thus, it seemed that spontaneous respiration was a safety factor, as precipitous blood pressure drops to zero only occurred when controlled respiration with a high vaporizer setting was employed.

It was found very easy to take over control of the respiration without the need of relaxants, and when it was desired the patient would also resume control within a very short time.

At the termination of surgery, when the Fluothane was being blown off with a high flow of N_2O/O_2, respiration always slowed and deepened, with resumption of normal minute volumes.

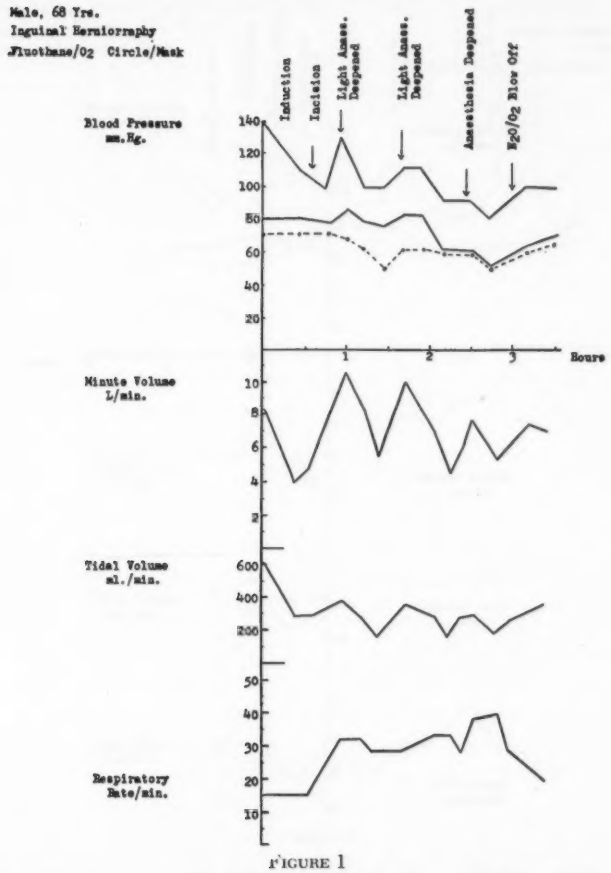

FIGURE 1

Fluothane in asthma. One patient had audible bronchospasm preoperatively. After five minutes of Fluothane the bronchospasm disappeared and did not return until several hours postoperatively.

Bronchial secretion. Markedly diminished, though several patients appeared to cough up tenacious sputum for several days postoperatively.

Muscular System

During induction there was frequently a transient period of generalized muscle rigidity which gradually relaxed.

In general, muscle relaxation was only fair to moderate, and attempts to increase it were limited by hypotension. Most lower abdominal incisions could be closed without relaxants, but upper abdominal incisions generally required a relaxant. However, it was noted that after about three hours of Fluothane administration, relaxation improved and often was equal to that seen in spinal

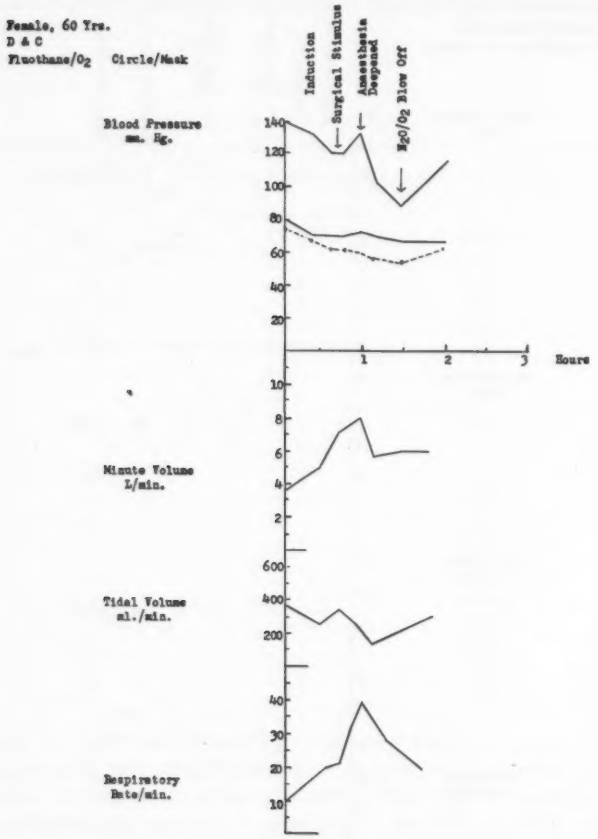

FIGURE 2

anaesthesia. In these cases respiration was controlled, which may have added to the effect.

On emergence a not infrequent phenomenon was a short period of muscle rigidity in the form of intense shivering. In several patients it was extremely violent and the patient's respiratory muscle spasm temporarily caused complete apnoea.

Effect of Muscle Relaxants

Succinylcholine and C_{10} acted in their usual brief fashion, but d-tubo curare and gallamine usually had relatively brief actions lasting on the average only ten minutes. On many patients 60 mgm. doses of gallamine produced no perceptible effect. Consequently, patients requiring continuous relaxation needed large total dosages of these two drugs.

No hypotension was noted which was directly attributable to the use of d-tubo curare and Fluothane, as reported by Johnstone. Seven patients were given

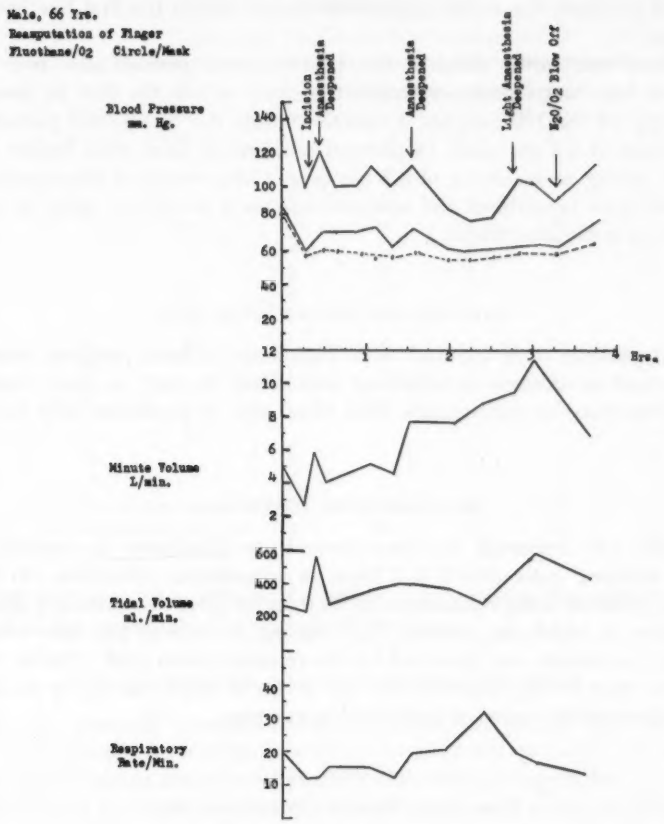

FIGURE 3

d-tubo curare in total dosages ranging from 9 mg. to 27 mg. without any blood pressure change whatsoever.

SKIN

In all patients the skin became warm, dry and pink as it does following spinal anaesthesia.

ALIMENTARY CANAL

During most abdominal procedures the gut appeared to be constricted during administration of Fluothane.

VOMITING

The multitude of factors associated with anaesthesia and surgery make the exact cause of postoperative vomiting difficult to assign. However, it is probable

that most vomiting due to the anaesthetic occurs within the first few hours after operation.

We have arbitrarily divided the postoperative period into two groups: one up to four hours postoperatively; the other within the first 24 hours postoperatively. Of the 120 patients, 4 vomited within the first 4-hour period, giving an incidence of 3.3 per cent; 14 patients vomited at some time within the first 24 hours, giving an incidence of 8.5 per cent. (Since many of these patients had intra-abdominal procedures and received opiates it would be unfair to attribute all vomiting to the anaesthetic.)

Salivary and Mucous Secretions

Several patients were induced with Fluothane without previous atropine or hyoscine and no increase in secretions was noted. In fact, in many cases belladonna drugs may be unnecessary. This effect was of particular help in thoracic surgery.

Recovery from Anaesthesia

Raventós (2) reported recovery time from Fluothane in animals to be 10 to 20 minutes, even after 5 to 6 hours of anaesthesia. Johnstone (3) likewise described patients being rousable some 10 minutes after discontinuing Fluothane.

The time at which the patients first reacted, as well as the time when they were fully conscious, was recorded by the recovery room staff (Tables III, IV). The latter were totally unaware that any series of cases was being studied and so their observations were not influenced in any way.

TABLE III

Time until Reacting Postoperatively

Time until reacting postoperatively (minutes)	Duration of surgery in hours				
	0–1	1–2	2–3	3–4	4–5
Under 15	6	2	2	1	–
15	10	7	6	2	2
30	4	5	3	2	1
45	3	1	3	–	1
60	–	1	1	1	–
75	–	3	–	–	–
90	–	–	2	–	1
105	–	–	–	–	–
120	–	1	–	–	–

From Table III it is seen that of the 71 cases studied for reacting time, the majority were reacting within the first 30 to 45 minutes postoperatively, and were conscious in an average of 60 minutes after completion of surgery (Table IV). It can be seen that increasing duration of anaesthesia was associated with in-

TABLE IV

TIME UNTIL CONSCIOUS POSTOPERATIVELY

Recovery time (hours)	(minutes)	Duration of surgery in hours 0–1	1–2	2–3	3–4	4–5
	5	1	–	1	–	–
	15	11	3	2	1	–
	30	10	10	4	4	–
	45	4	7	1	2	1
1		5	6	6	1	3
1	15	3	2	3	1	–
1	30	–	5	2	2	–
1	45	–	1	–	–	–
2		1	3	4	–	–
2	15	–	–	–	–	–
2	30	–	3	–	–	–
2	45	–	–	1	–	–
3		2	–	–	–	1
Over 3		1	–	–	1	1
Number of cases		38	40	24	12	6
Average time in minutes		50	60	65	65	105

creasing recovery time, though the difference between the groups was most marked in the procedures lasting four to five hours.

CONTROLLED HYPOTENSION WITH FLUOTHANE

Although generally speaking bleeding from small vessels was minimal with Fluothane anaesthesia despite normal or near normal pressures, it was further minimized for plastic and other operations with satisfactory results.

It proved to be easier to maintain the blood pressure evenly at 65 or 70 mm. Hg than at 100 mm. Hg. For this reason and also because blood pressure can be so readily raised, Fluothane was frequently requested when minimal bleeding was required.

DEATHS

There was only one death in the series occurring within one month of operation. This was an 84-year-old male who had a subtotal gastrectomy for a carcinoma of stomach. He died 26 days postoperatively, and autopsy revealed pulmonary infarction, pulmonary abscess and a terminal pneumonia.

No connection could be found between his death and the anaesthetic procedure.

SERIES II: USE OF FLUOTHANE IN THE SEMI-CLOSED SYSTEM

METHOD

In this series of cases Fluothane was administered to 190 patients. The patients were premedicated with the usual agents—morphine or Demerol, together

with a belladonna drug, with the exception of craniotomies, where belladonna drugs alone were given. In few cases phenergan or barbiturates were added to the premedication. Pentothal® in doses of 100 to 500 mgm.—average 200 to 250 mgm.—was routinely injected for induction. When endotracheal technique was indicated, succinylcholine was administered in doses of 60 to 100 mgm. to facilitate intubation. All the patients were maintained on a semi-closed system with a 10-litre flow of gas, either oxygen or oxygen and nitrous oxide in 50-50 concentration. Most of the patients were allowed to breathe spontaneously with little or no assistance to respiration. The age group of these patients ranged from 6 days to 83 years.

Types of Cases

Neurosurgical	67	36.2%	Urological	14	7.6%
Laparotomies	20	10.4%	Thoracic	7	3.6%
General surgical	31	16.0%	Orthopaedic	9	4.6%
Gynaecological	32	16.6%	Plastic	6	3.1%
		Endoscopic	4	2.1%	

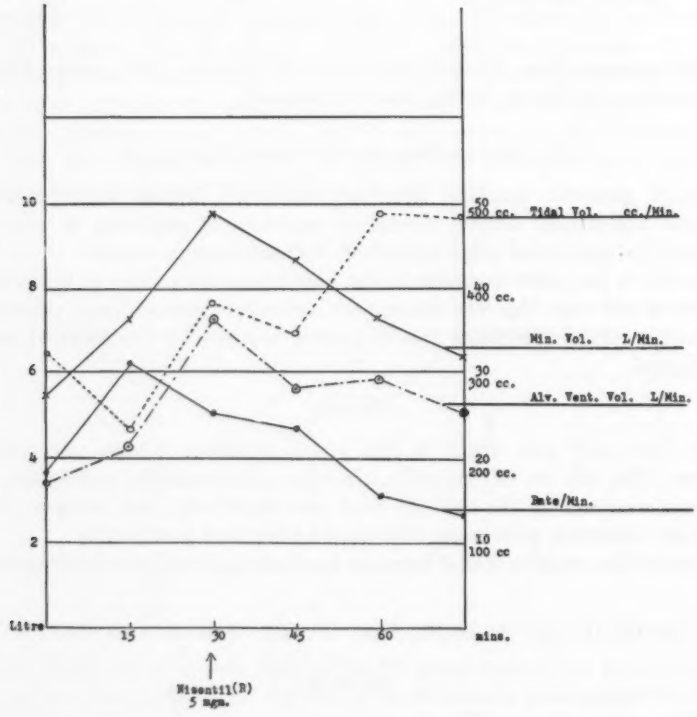

Figure 4

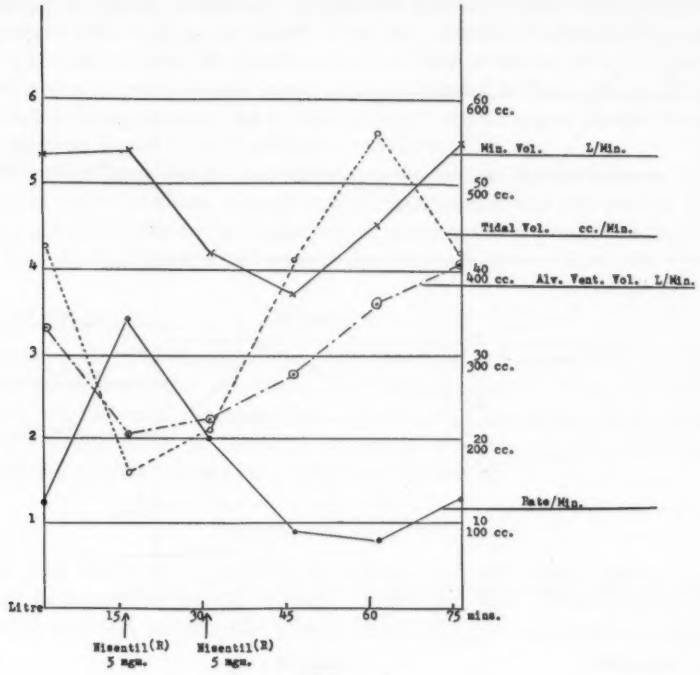

FIGURE 5

RESULTS

Induction was usually carried out rapidly with Pentothal®, and Fluothane was added slowly to the semi-closed circuit. Fluothane caused little excitement during the induction period. Adequate surgical anaesthesia was usually established in about five minutes. There was little or no laryngospasm or bronchospasm with increasing concentration of the agent.

RESPIRATORY SYSTEM

Fluothane had a marked effect on the respiratory function under anaesthesia. In practically all the cases the rate of respiration was increased to a greater or lesser extent. Respiratory rates as high as 50 per minute were noted. The tidal volume fell in an inverse relation to the rate: that is, as the rate of respiration increased the respiration became shallower. If the rates of respiration were decreased by the use of an opiate, the respiration became deeper. In this series of cases Nisentil in doses of 5 to 15 mgm. was given either intravenously or intramuscularly to reduce the tachypnoea during anaesthesia. These changes are illustrated by the accompanying graphs (Figs. 4, 5 and 6). During anaesthesia there was no stimulation of secretion in the respiratory tract. The respiration during anaesthesia appeared to be adequate in patients with spontaneous respira-

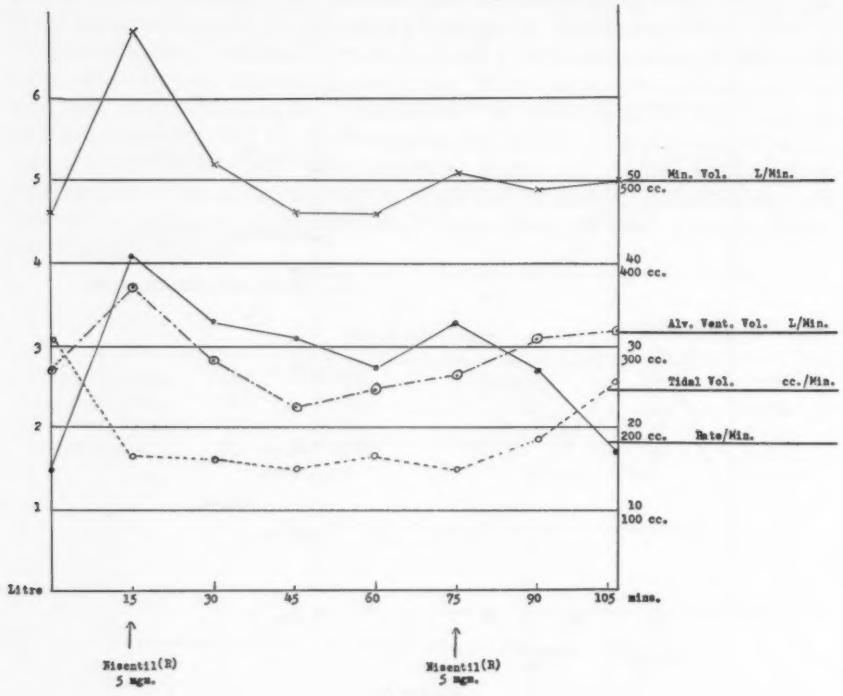

FIGURE 6

tion. The minute volume was slightly increased or decreased as illustrated, while the tidal volume varied inversely with the rate. In most of the cases endotracheal technique was used so that the dead space was reduced by at least one-third; thus efficient respiration could be maintained with a smaller minute and tidal volume.

CARDIOVASCULAR SYSTEM

The cardiovascular effect of Fluothane appeared to be the major limiting factor of the agent. A rapid increase in concentration of the vapour, or deep anaesthesia, decreased the blood pressure. The blood pressure could be decreased very rapidly and there were two cases where rapid increase in concentration dropped the blood pressure to unrecordable levels. In most of the cases under surgical anaesthesia, the blood pressure was maintained with no marked fall.

B.P. fall during anaesthesia	*Per cent*	*Postoperative B.P.*	*Per cent*
Less than 20 mm. Hg	58	Above preoperative	43
21 to 40 mm. Hg	30	Less than 20 mm. Hg below	43
Over 40 mm. Hg	12	21 to 40 mm. Hg below	12.5
		Over 40 mm. Hg below	1.5

There was little depression of the blood pressure during the immediate post-operative period as shown by the above chart. The blood pressure changes could

be attributed to central action, as a ganglionic blocking agent still reduced the blood pressure with varying sensitivity, from very sensitive to relatively resistant. Arfonad was used to lower the blood pressure on five occasions with no difficulty. In a small series of seven thoracotomies, there appeared to be a greater difficulty in maintaining blood pressure. As a rule the blood pressure level settled to about 60 mm. Hg even under light Fluothane anaesthesia.

The occasional arrhythmias encountered were minor. Bradycardia was commonly found with Fluothane though in most instances it was not severe. Therefore, extra atropine prior to the induction of anaesthesia was not essential. With marked bradycardia atropine will reverse the slow rate.

Relaxation

Relaxation under Fluothane varied with the depth of anaesthesia. In lighter planes of anaesthesia the relaxation was only moderate. With spontaneous respiration, relaxation of the abdominal muscles was moderate, often requiring the aid of relaxant drugs to facilitate closure of the peritoneum. The masseter muscle was adequately relaxed for purposes of intubation.

Nausea and Vomiting

Nausea and vomiting is probably less than with the other agents. In the immediate postoperative period—4 hours—only 8 per cent of the patients were nauseated or vomited, while in the first 24 hours, 13.7 per cent were nauseated or vomited.

Recovery Time

As a general rule the recovery from an anaesthetic varies with the duration of the operation. Where Fluothane was used, the time of emergence from anaesthesia depended on the duration of anaesthesia. Where the procedure was less than one hour, the average time for regaining complete consciousness was 37 minutes, for cases between one and three hours, 70 minutes, and over three hours it was 90 minutes.

Deaths

There were five postoperative deaths in this series. None of the deaths was related to anaesthesia. Two deaths followed craniotomy for brain tumour; one death was from a myocardial infarction eleven days after a Smith-Petersen nailing of the hip; one death from massive haemorrhage during a thoracotomy, and the final death followed a thoracotomy for advanced bronchogenic carcinoma.

Discussion

The non-irritant properties of Fluothane made induction with it reasonably pleasant, though being relatively slow it is less convenient than thiopentone induction.

However, in Series I, Fluothane induction served to demonstrate its true cardiovascular and respiratory effects.

The cardiovascular effects of Fluothane are mainly hypotension and bradycardia, associated with cutaneous vaso-dilatation. Venous dilatation occurs early, facilitating venepuncture.

The severity of the hypotension and bradycardia is directly proportional to the rate and magnitude of the increase in vapour concentration.

Induction hypotension was less marked using a semi-closed technique, with only 12 per cent of the patients having a systolic drop of more than 40 mm. Hg, compared to 33 per cent with the closed circuit.

Again it is noted that 10 per cent of the patients anaesthetized with the closed technique had blood pressure falls to unrecordable levels, as opposed to only 1 per cent anaesthetized with a semi-closed technique. With the latter technique, using a high gas flow, Fluothane concentration can be kept relatively constant, and it is probably the technique of choice.

Atropine, by causing a tachycardia, will tend to minimize the initial induction hypotension, but is probably of value mainly in the older age group. During maintenance, intravenous atropine is quite effective in raising blood pressure when it is low, the rise not being above preoperative levels. Thus the use of atropine may permit a deeper plane of anaesthesia to be reached, when depth would otherwise be limited by the hypotension.

One cardiac arrest occurred in the series, reminding us of the vigilance with which blood pressure levels must be watched.

The decrease in bleeding constitutes one of the most important properties of Fluothane, especially as it does not appear to depend on hypotension.

With Fluothane, controlled hypotension is easily obtained and can be reversed very rapidly. If desired, Arfonad may be used with Fluothane to produce controlled hypotension in a lighter plane of anaesthesia.

Arrhythmias are fairly common, mainly in the form of extrasystoles and bigeminal rhythm, but disappear readily when the anaesthesia is lightened or atropine is used.

Postoperatively blood pressure is well maintained and over 80 per cent of patients had blood pressures not less than 20 mm. Hg below preoperative levels. With the semi-closed and closed techniques, 27 per cent and 43 per cent, respectively, had blood pressures above the preoperative level.

Respiration becomes rapid and shallow, though in the lighter planes it appears adequate, especially with the use of an endotracheal tube to reduce dead space. With deeper planes, the respiratory rate, though rapid, does not compensate for the decreased tidal volume, and thus minute volumes tend to be below normal. If respiratory rate is slowed with an opiate, the minute volume increases again owing to a greatly increased tidal volume. Thus, with respiratory rates of 30 per minute or over, respiration should either be assisted or slowed with an opiate.

In light planes of anaesthesia surgical stimulus causes a marked increase in respiratory rate and depth, resulting in large tidal and minute volumes. This respiratory change usually precedes reflex movement by the patient and allows anaesthesia to be deepened to prevent this.

As blood pressure is depressed early, anaesthesia may still be light even though hypotension has occurred, and at this time there may be the respiratory signs

of light anaesthesia. It is at this time that anaesthesia should be deepened with great caution.

The ease with which respiration can be controlled with Fluothane is one of its most desirable properties and is especially valuable in thoracic surgery. Since the patient will resume control of his own breathing when desired, there is no fear of respiratory depression from the use of relaxants.

An interesting sidelight in the investigation was the occurrence of low minute and tidal volume readings in the premedicated cases, many of which were surprisingly depressed.

Although only one patient with asthma was anaesthetized with Fluothane, the relaxation of bronchospasm produced suggests another possible advantage of this agent.

The decrease in bronchial secretions suggests a future for Fluothane in thoracic surgery, though there was an impression that with an open chest blood pressure was difficult to maintain.

Recovery from anaesthesia was assessed and there seemed to be an increase in the time taken to recover consciousness with increasing duration of surgery. The majority of patients were responding well within 45 minutes after anaesthesia was discontinued, and most were fully conscious after about 60 minutes. With procedures lasting 4 hours and more, consciousness was regained after approximately 90 minutes.

Relaxation generally could be described as moderate. Lower abdominal incisions could usually be closed without the need for a relaxant, but unless Fluothane had been administered for three hours or more, upper abdominal wounds required the use of one.

After three hours, with controlled respiration relaxation became excellent, and many surgeons commented favourably.

An interesting observation has been the brief duration of action of the curare-type relaxants. The explanation for this is unknown.

Postoperative vomiting is probably much less than with other agents. In the closed circuit series, 3.3 per cent of the patients vomited within the first four hours postoperatively, and 8.5 per cent within the first 24-hour period. The corresponding figures in the semi-closed series were 8 per cent and 13.7 per cent respectively. It should be recalled that more than half were neurosurgical cases.

Generally speaking, the authors feel that Fluothane has sufficient desirable properties to justify its inclusion in the anaesthetist's armamentarium, though further work on the possible metabolic effects is needed.

Because it causes a profound depression of the cardiovascular system, Fluothane probably should be used only by the experienced anaesthetist. We do not feel it is suitable with present-day equipment for the occasional anaesthetist. Although some means of knowing the exact concentration in the circuit would be interesting and safer, differences in individual sensitivity to Fluothane could still occur. Therefore, the blood pressure reading is still the most important guide to the patient's safety.

We feel that Fluothane will be used mostly in neurosurgery, plastic and radical surgery, and certain cases involving an explosion hazard.

SUMMARY

A series of 310 cases is presented in which Fluothane® has been administered, using both the closed and semi-closed techniques.

The chief advantages of Fluothane® are:

1. Non-explosibility.
2. Can be used in the presence of soda lime.
3. Non-irritating to breathe.
4. Diminished salivary and bronchial secretions.
5. Diminished bleeding without the need for extreme hypotension.
6. Can be used as a reversible hypotensive agent.
7. Allows respiration to be readily controlled.
8. Moderately rapid recovery.
9. Low incidence of postoperative vomiting.
10. Low incidence of postoperative hypotension and shock.

The chief disadvantages are:

1. Cardiovascular depression, often of severe degree.
2. Respiratory depression with moderately light anaesthesia. Apnoea with deeper planes.
3. Frequently causes cardiac arrhythmias.
4. Relaxation generally only moderate.
5. Incompatible with epinephrine and norepinephrine.

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OBSERVATIONS CLINIQUES SUR L'ANESTHESIE AU FLUOTHANE*

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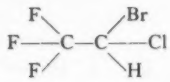
AVEC PLUSIEURS MODALITÉS de techniques et différents appareils, le Département d'Anesthésie de l'Hôtel-Dieu de Québec a utilisé le Fluothane pour 1,112 interventions chirurgicales chez des patients de différents âges.

Le Fluothane, un anesthésique volatil, est un éthane halogéné, le 2-bromo-2-chloro-1-1-1-trifluoro-éthane, qui a pour formule chimique:



PROPRIÉTÉS PHYSIQUES, CHIMIQUES ET PHARMACOLOGIQUES

C'est un liquide clair, incolore, d'odeur particulière. Il est non-inflammable, non-explosif. C'est un composé stable, mais théoriquement, en présence d'air, d'humidité et de lumière, il peut, à la longue, se décomposer en acides variés du groupe halide. Les produits de décomposition peuvent affecter certains métaux, tels que l'étain et l'aluminum. Il peut être fixé par le caoutchouc, l'amollir et l'enfler. Le caoutchouc revient lentement à son état normal quand il est exposé à l'air. Cliniquement, ces produits de décomposition n'ont pas d'effets nocifs, bien qu'ils soient théoriquement nuisibles. Le thymol, dans la proportion de 0.01 pour cent ajouté au Fluothane, le stabilise à l'action de la lumière. De même, l'emmagasinage dans un endroit frais et dans des bouteilles ambrées éloignent à l'infini les possibilités de décomposition. Le Fluothane est stable au contact de la chaux sodée froide ou chaude et peut être administré en circuit fermé avec absorption de CO_2, sans qu'il y ait formation de produits toxiques de décomposition. Sur la peau, cet anesthésique ne produit pas la sensation de brûlure ressentie après l'application d'éther ou de chloroforme. Il n'irrite pas la muqueuse buccale, laryngée et trachéale. Il ne cause pas d'œdème pulmonaire. Son index thérapeutique est deux fois celui de l'éther, dont il a quatre fois la puissance. Sa marge de concentration anesthésique va de 1 à 3 pour cent (1,2,3).

Le Tableau I permet de comparer les caractères physiques et chimiques du Fluothane avec le chloroforme, l'éther, le Vinéthène, le Vinamar et le Fluoromar.

*Le Fluothane a été fourni par Ayerst McKenna, Montréal. Date d'adresse pour publication: 27 avril 1957.

†Les docteurs Lauréat Jean, Jean-Louis Boivin, Pierre-Paul Paquet, André McClish, Jacques Pelletier et Egbert Daigle ont collaboré à l'étude de cet anesthésique.

TABLEAU I

Anesthésique	Type	Formule chimique	Poids moleculaire	Point d'ébullition	Gravité specifique liquide (eau = 1)	Solubilité dans 100 parties d'eau	Solubilité huile–eau 37° C	Limite d'inflammibilité		Tension de vapeur à 20° C mm. Hg
								Air	O_2	
Chloroforme	Hydrocarbone chloré	$CH\,Cl_3$	119.39	61.26	1.49	0.822	100			160.5
Ether	Diethyl-éther	$(C_2H_5)_2O$	74.12	34.6	0.713	7.5	3.2	1.85 36.5	2.10 82.0	439
Vinethène	Divinyl-éther	$(C_2H_3)_2O$	70.9	28.3	0.774	4.0	41.3	1.7 27.0	1.85 85	
Vinamar	Ethyl-vinyl-éther	$C_2H_5—O—C_2H_3$	72.10	35.8	0.759		45		21	4.85
Fluoramar	Hydrocarbone fluore	$CF_3—CH_2—O—CH—CH_2$	126.0	42.7	1.13	0.4	94	30		
Fluothane	Ethane halogéné	$CF_3—CHBrCl$	197.39	50.2	1.86	0.345	330	Non-inflammable avec O_2 de 0.5 à 50.0		243

Etudes statistiques

Le Fluothane a été administré avec plusieurs modèles d'appareil à anesthésie: Heidbrink avec bouteille no 7 de vaporisation à mèches sur l'inspiration ou sur l'expiration; Marrett, Boyle, en circuit fermé ou semi-fermé; McKesson, E.M.O., appareil de Friedman; appareil pour enfants M.I.E. La valve de Fink a servi à mesurer la ventilation pulmonaire au cours de l'anesthésie.

Le Fluothane a été utilisé seul avec le protoxyde d'azote–oxygène ou dans des séquences variées.

Combinaisons anesthésiques

N_2O+O_2+Fluothane	817
Néraval$+N_2O+O_2+$Fluothane	92
Pentothal$+N_2O+O_2+$Fluothane	181
N_2O+O_2+Fluothane$+C_3H_6$	7
N_2O+O_2+Fluothane$+(C_2H_5)_2O$	4
Fluothane+locale du genou	1
Fluothane+bloc brachial	4
Fluothane+rachidienne	3
Fluothane+caudale	1
Fluothane+Viadril	2
	1,112

Sous anesthésie au Fluothane 1,112 interventions chirurgicales d'une durée variable ont été pratiquées chez des patients de tout âge et des deux sexes (514 hommes, 598 femmes).

Plusieurs sujets ont été anesthésiés plus d'une fois au Fluothane à un intervalle de quelques jours à quelques semaines (57 deux fois, 5 trois fois, et un quatre fois).

Un grand nombre de patients n'ont pas reçu de médication pré-anesthésique et pour les autres, la prémédication n'a pas dérogé à celle habituellement donnée pour les autres formes d'anesthésies générales.

L'examen pré-opératoire a montré la présence de certains troubles physiologiques chez certains individus: emphysème pulmonaire, sclérose pulmonaire, bronchite, asthme, rétrécissement mitral, endocardite chronique, sclérose coronarienne, infarctus ancien, bloc de branche, surcharge ventriculaire, diabète, troubles vasculaires des extrémités.

Etudes cliniques

L'étude de la marche de l'anesthésie et de l'action du Fluothane sur le système nerveux central et autonôme, sur l'appareil cardio-respiratoire et sur le système rénal donne une idée assez concrète de l'utilisation clinique de ce nouvel anesthésique volatil.

Induction et maintien de l'anesthésie

L'anesthésie au Fluothane avec protoxyde d'azote–oxygène (5 litres–5 litres ou 3 litres–3 litres selon l'appareil utilisé et la technique employée) doit être lente, graduelle, progressive et non subite de façon à maintenir la concentration

Interventions chirurgicales

Ophtalmologie	33
Oto-rhinolaryngologie	467
Chirurgie générale	335
Gynécologie	95
Urologie	64
Orthopédie	118
	1,112

Ophtalmologie

Cautérisation cornée	2
Straborexie	8
Rétinopexie	2
Dilatation des voies lacrymales	4
Ptose des paupières	3
Ablation de chalazion	2
Dacryocystorhinostomie	1
Tension oculaire	2
Résection sclérale	1
Enucléation	4
Iridosinéchotomie	1
Discission œil	1
Plastie orbite	2
	—
	33

Oto-rhinolaringologie

T+A	324
Lavage de sinus	12
Paracentèse	13
Résection sous muqueuse	21
Plastie nasale	9
Caldwell-Luc	9
Œsophagoscopie	11
Mastoïdectomie	9
Fenestration	8
Bronchoscopie	5
Laryngoscopie	4
Cure sinus frontal	1
Ligature loge amygdalienne	2
Plastie oreille	4
Trachéotomie	3
Déméchage mastoïdectomie	6
Extraction cérumen	2
Abcès oro-pharyngée	7
Ablation glandes salivaires	3
Résection diverticule de l'œsophage	1
Aspiration bronchique	5
Extraction dentaire+obturation	8
	—
	467

Chirurgie générale

Appendicectomie	34
Cholecystectomie	23
Cholecysto-duodénostomie	1
Herniotomie inguinale	20
Gastrectomie	8
Gastro-enterostomie	2
Gastrostomie	2
Vagotomie	1
Anus artificiel	4
Sigmoïdectomie	3
Adhérences	1
Duodeno-jejunostomie	1
Résection intestinale	2
Hemicolectomie	2
Diverticulectomie	1
Abdomino-perinéale	2
Biopsie épiploon	1
Hépatectomie partielle	1
Polypectomie par voie abdominal	1
Fermeture anus artificiel	1
Ablation drainage abdominal	8
Herniotomie ombilicale	6
Eventration	11
Herniotomie crurale	1
Hemorroïdectomie	6
Abcès anal	8
Rectoscopie	3
Mastectomie	20
Staphyloplastie	17
Thyroïdectomie	13
Biopsie du sein	9
Abcès du sein	4
Stripping	8
Sympathectomie lombaire	2
Surrènalectomie	1
Réparation plaie visage	12
Ablation tumeur cutanée	10
Abcès temporal	2
Panaris	40
Anthrax	10
Hydrosadénite	9

Chirurgie générale (cont.)

Biopsie ganglion cervical	6
Evidement cervical	5
Kyste cervical	1
Ligature artère occipitate	1
Biopsie langue	2
Ablation points superficiels	2
Kyste pilonidal	2
Greffe cutanée	5
	335

Gynécologie

Examen gynécologique curetage utérin	47
Hystérectomie	29
Colpopérinéorraphie	10
Wertheim	2
Vulvectomie	1
Ovariectomie	3
Abcès glande de Bartholin	1
Cotte	1
Salpingo-ovariectomie	1
	95

Urologie

Cystostomie	3
Castration	1
Cystectomie	1
Retournement vaginale	3
Uretéro sigmoïdostomie	1
Prostatectomie	3
Néphrectomie	2
Pyelotomie	1
Pyelographie	1
Lombotomie	1
Cystoscopie	23
Circoncision	24
	64

Orthopédie

Ponction moelle osseuse	3
Bursectomie	5
Costotomie drainage thoracique	4
Réduction sanglante	31
Pied bot élongation tendineuse	9
Réparation de doigt	5
Torticolis	1

Orthopédie (cont.)

Résection osseuse	12
Platre jambe	9
Kyste synovial poignet	4
Luxation maxillaire	1
Menisectomie genou	7
Saucérisation fémur	1
Amputations	8
Ablation broche de Kirschner	5
Corset platré	2
Laminectomie	1
Hallux valgus	1
Débridement plaie	9
	118

Âge

0– 6 mois	7
6 mois– 1 an	23
1– 5	134
5–10	154
10–15	56
15–25	161
25–35	144
35–45	133
45–65	220
65–75	70
75–85	10
	1,112

Durée

0–30 minutes	246
30–45	378
45–60	128
1– 2 heures	233
2– 3	84
3– 4	28
4– 5	10
5– 6	5
	1,112

Prémédication

Aucune	111
Atropine seul	16
Codéine+atropine	2
Morphine+atropine	417
Morphine+atropine+bénadryl	13
Morphine+atropine+pacatal	6
Morphine+atropine+stémétil	1
Démérol seul	3
Démérol+atropine	459
Démérol+atropine+bénadryl	3
Lévodromoran seul	1
Lévodromoran+atropine	16
Lévodromoran+atropine+bénadryl	43
Lévodromoran+atropine pacatal	20
Lévodromoran+atropine+sparine	1
	1,112

dans les limites de 1 à 3 pour cent et à conserver une ventilation pulmonaire adéquate tout en surveillant le pouls et la tension artérielle. En l'absence d'un vaporisateur calibré en pourcentage, une bouteille de vaporisation d'éther no 7 avec mèches a été utilisée sur l'appareil Heidbrink; elle est ouverte graduellement jusqu'au chiffre 4 pour être ramenée entre les chiffres 2 et 3 comme dose d'entretien. Sur les appareils Marrett et Boyle, le Fluothane est placé dans la bouteille à trilène qui est ouverte à peu près aux mêmes chiffres; le plongeur sur la bouteille à trilène de la Boyle étant complètement levé.

La phase analgésique semble inexistante. La deuxième phase est différente de celle de l'éther: il n'y a pas d'incohérence, de délire, de larmoiement, de cris, de toux, d'éternuements, d'éructations, de nausées, de vomissements, de secrétions salivaires et trachéo-bronchiques, de convulsions. La phase chirurgicale est atteinte en quatre à huit minutes. L'intubation se fait librement sans déterminer des mouvements de toux ou de bucking, et le plus souvent sans l'aide d'un curarisant.

Pas d'intubation	377
Intubation avec N^2O + O^2 + Fluothane	486
Intubation avec N^2O + O^2 + Fluothane + curarisant	249
	1,112

Si l'induction se fait avec un thiobarbiturique, pentothal ou néraval avec ou sans relaxants, l'apport du Fluothane dans la séquence anesthésique ne doit se faire qu'au moment du retour de la stabilisation de la tension artérielle, du rythme respiratoire régulier et efficace à son inhalation appropriée.

En se basant sur certains signes anesthésiques évidents, il appert que le Fluothane ait une action ganglioplégique: que le patient ait eu ou non une prémédication, la pupille oculaire demeure punctiforme et ne se dilate pas progressivement comme au cours de l'approfondissement de l'anesthésie à l'éther. Les conjonctives se congestionnent. Il y a absence complète de diaphorèse, suppression des secrétions salivaires et trachéo-bronchiques. La peau est rose

chaude et sèche. Il y a vaso-dilatation périphérique (4). Il n'y a pas de hoquet, de laryngospasme, de bronchospasme. Chez un malade non intubé, un stridor laryngé a été observé en anesthésie profonde au cours d'une ostéosynthèse du tibia. Ce stridor est disparu en diminuant la concentration de l'anesthésique. Le hoquet qui apparait parfois au cours des gastrectomie sous anesthésie au thio-barbiturique–curare–protoxyde d'azote–oxygène ne s'est pas produit avec le Fluothane.

Respiration

Pendant l'induction ou au cours du maintien de l'anesthésie au Fluothane, il faut éviter toute dépression respiratoire tant dans l'amplitude que dans la vitesse. Si la profondeur et le rythme respiratoire sont tous deux susceptibles d'être diminués lors de l'induction, c'est surtout l'amplitude qui peut devenir inefficace pendant le maintien. Cette dépression respiratoire peut entrainer l'hypoxie, la rétention de CO_2 et la cyanose non par bronchoconstriction mais par défaut de ventilation adéquate, et des irrégularités cardiaques. Au cours des fénestrations, interventions où le rythme respiratoire est peu influencé par le stimulus chirurgical, le volume minute s'est maintenu en moyenne à 4½ litres. Ceci signifie que dans une grande proportion de cas la ventilation doit être assistée.

L'amplitude demande à être surveillée attentivement et à être aidée par une ventilation assistée raisonnée. Au début de l'anesthésie, si l'amplitude est assistée trop fortement, surtout chez l'enfant, il peut s'établir une surdose anesthésique toxique pour le cœur qui avec le Fluothane semble saturé avant le cerveau à l'instar d'ailleurs du chloroforme et à l'inverse de l'éther qui sature d'abord le cerveau (6). La respiration assistée pratiquée trop longtemps ou cinq à six mouvements de respiration contrôlée avec une concentration élevée de Fluothane peuvent entrainer une chute de la pression artérielle. Pendant la ventilation assistée ou contrôlée, la concentration du Fluothane doit être réduite.

La distension vésicale et certains stimuli chirurgicaux peuvent causer une tachypnée, tachypnée surtout apparente chez les jeunes adultes. Il semble que les réflexes centraux de la respiration ne soient pas abolis. Le Démérol, à petites doses, corrige la tachypnée due au stimulus chirurgical. Avec le Fluothane, la ventilation assistée est libre et facile; la résistance à la ventilation assistée est toujours absente durant l'induction, le maintien et le réveil.

Circulation

Le Fluothane a une action caractéristique sur la circulation. Le pouls ralentit à 70 ou moins. La pression artérielle baisse de 20 pour cent dans la majorité des cas. Cette hypotension est sous la dépendance de la profondeur de l'anesthésie et du degré de sympathicotonie du sujet. Mais au fur et à mesure que l'anesthésie s'étend dans le temps, cette hypotension devient de moins en moins importante et la tension se maintient légèrement sous la normale.

Avec le Fluothane, l'action vagale sur le cœur est prédominante. Cette prédominance favorise le déplacement du pacemaker et l'apparition d'un rythme nodal. La dépression du nœud sino-auriculaire peut rendre possible les décharges

des centres ectopiques. Ces arythmies surviennent au cours d'une induction rapide et dans les stades profonds de l'anesthésie. Elles disparaissent avec la diminution de la concentration du Fluothane et avec la correction de l'hypoxie de ventilation si elle existe. Elles ont été rencontrées dans 14 pour cent des électrocardiogrammes enrégistrés.

Il y a donc avantage et nécessité d'utiliser un vaporisateur donnant une concentration connue de fluothane et limitée à 3.5 pour cent de maxima (5). Les troubles du rythme rencontrés dans cette série de 1,112 cas ont été du type nodal, nodal supérieur, bradycardie légère, bigéminisme, trigéminisme, extrasystoles ventriculaires.

Les cas de coronarite, d'infarctus ancien, de cor pulmonale n'ont pas semblé être mal influencés par l'administration de Fluothane. Les emphysémateux avec hypertension veineuse ont paru s'améliorer temporairement pendant l'anesthésie et dans les heures qui suivirent.

Des tracés électrocardiographiques ont été enrégistrés au cours d'anesthésie prolongée au Fluothane, comme les fénestrations.

Voici le rapport des docteurs Georges Saulnier et Jean Beaudoin, cardiologues du service de médecine de l'Hôtel-Dieu: résumé des différentes constatations faites sur l'étude de 30 électrocardiogrammes enrégistrés au cours de l'anesthésie au Fluothane.

1. *Tracé pré-opératoire*
   I. 21 tracés strictement normaux.
   II. 9 tracés anormaux se répartissant ainsi:
      (*a*) tachycardie sinusale à 142, 1 cas.
      (*b*) extrasystolie, 1 cas.
      (*c*) augmentation de l'amplitude l'onde P; hypertrophie auriculaire droite possible, 1 cas.
      (*d*) modifications non spécifiques de la phase terminale, créant des électro dit "limite," 6 cas.

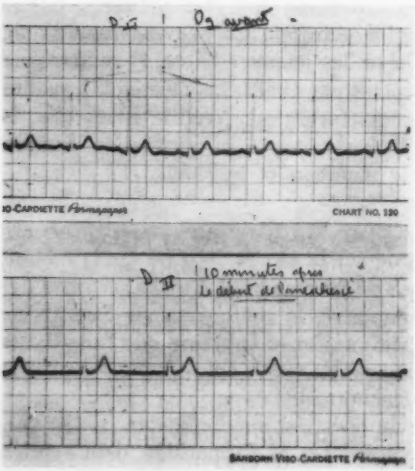


FIGURE 1

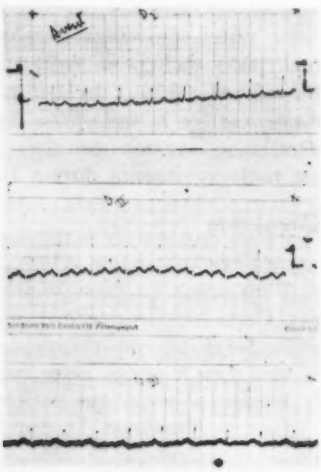


FIGURE 2

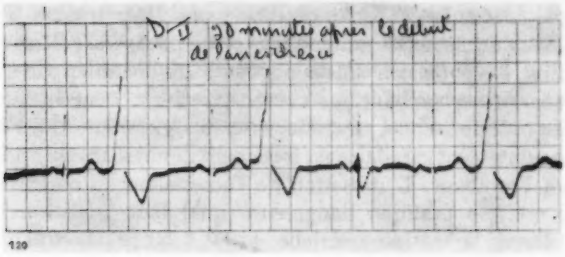


FIGURE 3

2. *Tracé per-opératoire*

I. Dans la plupart des cas, il y a un ralentissement modéré du rythme cardiaque.

II. Les tracés anormaux n'ont pas été modifiés en cours d'anesthésie.

III. Quatre modifications électriques méritent d'être rapportées:

(*a*) apparition d'un rythme nodal, 58/minute, 10 minutes après le début de l'anesthésie. Dans le tracé pris 20 minutes après le début de l'anesthésie, tout est entré dans l'ordre (Fig. 1).

(*b*) apparition de bigéminisme 20 minutes après le début de l'anesthésie, suivie par l'installation d'un rythme nodal supérieur (coronary sinus rythme), qui persiste 2 heures après le début de l'anesthésie (Figs. 2–4). Un électro fait 10 jours après l'intervention montre le retour au rythme sinusal.

FIGURE 4

(*c*) modification non spécifique de la phase terminale; ondes *T* aplaties ou inversées en D^2AVL, qui s'installent 2.45 heures après le début de l'anesthésie et persistent 4.45 heures après (anesthésie, durée: 5 heures).

(*d*) dans un cas, on note l'apparition d'extrasystoles ventriculaires après 10 minutes d'anesthésie.

Le Flaxédil, à petites doses répétées, donne une tachycardie plus évidente qu'avec les autres anesthésiques. Des doses répétées de Flaxédil ont parfois causé

une tachycardie à 150. Le Flaxédil ne donne pas l'hypotension du tubocurare, la pression s'élève de 10 à 15 millimètres, et le pouls s'accélère de 20 et plus selon la dose. Si l'hypotension existe au cours du maintien de l'anesthésie, il faut y remédier en recherchant ses causes possibles: concentration élévée de Fluothane, hémorragie subite, traction viscérale, position de Fowler, hyperventilation. Le suintement capillaire est fortement diminué même après trois heures d'anesthésie au Fluothane. L'utilisation de l'adrénaline au cours de l'anesthésie au Fluothane est une pratique dangereuse qu'il faut interdire. La distension vésicale peut élever la tension artérielle de 30 à 50 millimètres de mercure.

Médication adjuvante

Dans le but de contrecarrer certains effets secondaires du Fluothane sur la circulation, sur le rythme cardiaque: hypotension, extrasystoles, l'on a eu recours aux vagolytiques centraux, aux ataraxiques, au Pacatal, Bénadryl, Centrine, atropine et Démérol.

Sauf l'atropine et le Bénadryl par voie intraveineuse qui ont élevé légèrement la tension artérielle et accéléré le pouls, sans toutefois corriger complètement les irrégularités du pouls, la médication adjuvante n'a pas donné les résultats recherchés. Le Démérol produit un ralentissement de la respiration compensé

Médication adjuvante	
Aucune	905
Démérol	23
Atropine	38
Bénadryl	78
Pacatal	55
Arfonad	4
Diparcol	3
Centrine	4
Bénatrol	2
	1,112

mais insuffisamment par une augmentation de l'amplitude respiratoire. Cette médication ne peut pas remplacer une technique anesthésique minutieuse. Dans certains cas, seule la diminution de la concentration ou l'arrêt momentané du Fluothane out eu raison des irrégularités du pouls.

Système rénal

L'étude chez le rat soulignait que la fonction rénale n'était pas lésée par l'administration répétée de Fluothane (2). Chez huit cas de fénestration qui furent anesthésiés au Fluothane pendant 4½ heures environ, les examens urinaires le jour même de l'intervention et le troisième jour post-opératoire n'ont montré aucun signe pathologique: albumine, cylindres, densité anormale.

Relâchement musculaire

Le relâchement musculaire produit par le Fluothane est complet pour les interventions sous-ombilicales. Pour les interventions sus-ombilicales, le relâche-

ment n'est pas toujours satisfaisant et, avec le Fluothane seul, il ne peut être adéquat parfois qu'au dépens d'une hypotension importante ou d'un trouble du rythme cardiaque. D'habitude, il faut administrer 20 à 40 milligrammes de flaxédil, dose qui ne modifie pas ou peu la ventilation pulmonaire et donne le relâchement désiré sans exiger l'augmentation de la concentration du Fluothane.

Curarisants	
Aucun	837
Anectine	47
Anectine+syncurine	29
Brévidil	37
Brévidil+syncurine	20
Syncurine	2
Tubocurare	11
Flaxédil	129
	1,112

A la fermeture du péritoine, il n'est pas toujours nécessaire de répéter cette même dose. Avec l'expérience, le relaxant est manipulé selon le besoin. Le tubocurare, à cause de son action ganglioplégique, n'est pas à conseiller. Le succinylcholine et le décaméthonium, étant dénués d'effet hypotenseur, se prêtent bien à l'anesthésie au Fluothane, toujours cependant à la condition d'être administrés à faibles doses soit pour faciliter l'intubation ou accentuer le relâchement musculaire.

Réveil

Le réveil se fit entre cinq à vingt minutes après l'intervention. Le réveil est calme, l'état nauséeux se manifeste peu souvent et peut être attribuable à plusieurs autre facteurs. La tension artérielle se comporte tout comme si le sujet n'avait pas été anesthésié. L'état de la circulation est meilleur dans la période post-opératoire qu'à la suite de l'administration des autres anesthésiques. S'agit-il, dans le cas des autres anesthésiques, d'une dépression circulatoire consécutive à la stimulation circulatoire pendant l'anesthésie ou s'agit-il d'une accumulation sanguine post-opératoire dans le lit splanchnique? Par contre, dans le cas du Fluothane, s'agit-il d'une meilleure circulation dans les petits vaisseaux, d'une meilleure action sur le système nerveux autonôme: le malade ne présente ni cyanose des extrémités ni frisson, rien qui puisse ressembler au cyclo-choc. La tension artérielle et la circulation périphérique tendent à se maintenir à la normale; c'est ce qui a fait dire que le Fluothane avait une action antichoc (4).

L'anesthésie terminée, s'il y a présence d'un certain degré de curarisation et surtout s'il y a eu utilisation de 80 milligrammes ou plus de Flaxédil, il faut administrer prostigmine 1 milligramme et atropine 0.4 milligramme, sans négliger de continuer à assister la respiration pour l'élimination du Fluothane.

Période post-opératoire

Les jours suivants, il semble que les complications pulmonaires soient diminuées. Il a été noté que la fonction respiratoire des emphysémateux était améliorée pendant les premières heures (4). En considérant que les complica-

tions pulmonaires qui se manifestent le 2è, 3è, 4è jour ont, en réalité, débuté au réveil ou dans les heures suivantes, par la rétention des secrétions produites par les anesthésiques, par les effets muscariniques des relaxants, les drogues para-sympathico-mimétiques, les réflexes douloureux, en considérant d'autre part que le Fluothane déprime le réflexe de toux, déprime le réflexe de bronchoconstriction, même celui que produit le laryngoscope, la sonde endotrachéale (ce qui est très manifeste au cours d'une aspiration bronchique pratiquée sous Fluothane), que le Fluothane assèche complètement les secrétions salivaires et trachéo-bronchiques même chez les malades n'ayant reçu aucune prémédication, il est facile de supposer que l'atélectasie pulmonaire post-opératoire soit diminuée. L'étude des 1,112 cas semblent le prouver. Dix malades qui, les jours précédents, avaient eu un autre genre d'anesthésie pour leur intervention, ont subi une aspiration bronchique sous anesthésie au Fluothane. Dès que cessent l'aspiration et l'irritation causées par le cathéter bronchique, le malade reprend spontanément sa respiration normale sans toux, sans spasme et sans production de nouvelles secrétions. Ce procédé, en saturant le patient d'oxygène avant l'aspiration, facilite tellement la technique que le département d'anesthésie le préfère à toutes les autres méthodes employées auparavant: trans-trachéale, thiobarbituriques, N_2O-O_2-C_3H_6, anesthésie de surface des cordes vocales.

Dans les suites opératoires, les malades ne se sentent pas déprimés. Des malades ayant eu deux anesthésies pour fénestrations dont une au pentothal protoxyde d'azote–oxygène et l'autre au protoxyde d'azote–oxygène–Fluothane ont affirmé qu'avec le Fluothane, ils se sentaient moins déprimés le jour suivant. Est-il possible d'interpréter ce signe comme un état moindre d'intoxication, un état de sympathicotonie qui expliquerait l'effet antichoc et l'amélioration de la fonction pulmonaire.

Arrêt cardiaque

Au début de cette étude, deux cas d'arrêt cardiaque se sont produits, mais les patients ont récupéré normalement avec la thérapeutique appropriée:

1. *Femme de 40 ans,* en vagotonie marquée devant subir une mastectomie radicale. Prémédication: lévodromoran 2 milligrammes, atropine 0.4 milligramme; induction: Pentothal 250 milligrammes, succinylcholine 60 milligrammes; intubation puis passage sous respiration contrôlée au N_2O-O_2-Fluothane. La malade est placée en Trendelenburg renversé. Arrêt subit du cœur. Quatre minutes plus tard, massage cardiaque par thoracotomie. Le cœur est arrêté en diastole. Dès les premiers mouvements, le cœur se remet à battre. La malade présente quelques petits signes d'irritation corticale. Traitement: soluté glucosé hypertonique, infiltrations stellaires répétées, plasma. Le soir, la malade reprend conscience, les facultés intellectuelles ne semblent pas atténuées sauf un état confusionnel pendant 24 heures et perte de mémoire des faits nouveaux qui s'est rétablie dans les jours suivants.

Sept jour après elle subit sans aucun incident une mastectomie radicale qui dure deux heures. Prémédication: lévodromoran 2 milligrammes, atropine, 0.4 milligrammes, Pacatal 25 milligrammes; médication adjuvante: Pacatal 50 milligrammes, Bénadryl 50 milligrammes; induction et maintenance: N_2O-O_2-Fluothane-succinylcholine, 40 milligrammes. Evolution post-opératoire normale.

2. *Fille de 10 ans,* obèse, devant subir une appendicectomie d'urgence. Prémédication: déménol 50 milligrammes, atropine 0.3 milligramme. Induction: Pentothal 250 milligrammes, succinylcholine 60 milligrammes. Maintenance: intubation, N_2O-O_2-Fluothane sous respiration

contrôlée avec hyperventilation. A la sortie du cœcum, la tension artérielle de 120–80 tombe subitement; arrêt cardiaque. Comme il y avait résistance marquée à la respiration, l'anesthésiste venait d'administrer par voie intraveineuse: atropine 0.2 milligramme. Massage cardiaque par thoracotomie. Appendicectomie pratiqués. Aucune complication post-opératoire. Comment expliquer cet arrêt? La dose de pentothal était importante, la succinylcholine datait d'un mois: effet muscarinique possible; la résistance à la ventilation pouvait indiquer une décurarisation ou un effet muscarinique du relaxant; la respiration contrôlée avec forte pression positive diminuant le retour veineux; un certain degré d'hypoxie par la bronchoconstriction; l'action de la forte concentration du Fluothane sur le cœur, enfin le réflexe de traction sur le cœcum. Toutes ces causes semblent avoir contribué à l'arrêt cardiaque, spécialement la respiration contrôlée avec concentration élevée de Fluothane. Le cœur était dilaté et le chirurgien a dû pratiquer une dizaine de mouvements sur le cœur pour le ranimer, sans l'adjonction d'aucune drogue.

Les deux cas sont survenus dans les mêmes conditions avec les mêmes drogues, la même machine à anesthésie qui fut inspectée et trouvée défectueuse pour le débit d'oxygène. Il y a eu erreur de technique qui serait passée inapperçue avec un autre agent.

Depuis ce temps, la respiration contrôlée, surtout avec hyperventilation, a été abandonnée pour ne recourir qu'à la respiration assistée. L'emploi des curarisants a été modifié pour n'utiliser le plus souvent que de petites doses de Flaxédil.

Conclusion

Sur ces 1,112 cas anesthésiés au Fluothane, il n'y a pas de mortalité per-opératoire ou dans les quinze jours post-opératoires.

Trois cancéreux et un traumatisé de la colonne vertébrale sont décédés de l'évolution inexorable de leur état pathologique dans les suites post-opératoires éloingnées, ce qui permet raisonnablement d'écarter toute participation anesthésique:

1. *Homme, 53 ans,* fracture de L1-L2, section de la moelle terminale, troubles vésicaux et intestinaux.
   18 novembre 1956, Laminectomie. Anesthésie: Pentothal 325 mg., Flaxédil 60 mg., N_2O-O_2-Fluothane.
   3 décembre 1956. 15 jours après: broncho-pneumonie.
   3–4 décembre 1956. Aspiration bronchique.
   4 décembre 1956. 16 jours après l'intervention chirurgicale: décès, broncho-pneumonie terminale.

2. *Homme, 47 ans,* néoplasme du rectum depuis janvier 1956.
   8 février 1957. Anus artificiel. Anesthésie: N_2O-O_2-Fluothane, Flaxédil 20 mg.
   21 février 1957. Autre intervention. Anesthésie sans Fluothane.
   5 mars 1957. Décès, 25 jours après anesthésie au Fluothane, métastases généralisées.

3. *Femme, 48 ans,* néoplasme de la vessie.
   28 novembre 1956. Décaillotage de la vessie. Anesthésie: N_2O-O_2-Fluothane.
   21 janvier 1957. Décès, 54 jours après anesthésie. Métastases.

4. *Homme, 75 ans,* mélanôme achromique.
   4 décembre 1956. Cystostomie. Anesthésie: Néraval 625 mg., N_2O-O_2-Fluothane.
   3 février 1957. Décès, 61 jours après anesthésie au Fluothane. Métastases cérébrales.

Cette série de 1,112 anethésies au Fluothane permet les conclusions suivantes: le Fluothane a plusieurs avantages et des désavantages aisément contrôlables. C'est un anesthésique volatil puissant, d'action rapidement réversible, non-explosif, non-inflammable (il éteint lui-même la flamme). Il permet une induction facile, calme et bien acceptée. L'induction doit être lente, graduelle et progressive. Le maintien doit se faire avec douceur, sans hyperventilation, et sans augmentation brusque de la concentration avec un vaporisateur calibré à cette fin. C'est le meilleur moyen d'éviter l' hypotension néfaste, les irrégularités cardiaques et la dépression respiratoire que cet anesthésique est toujours susceptible d'engendrer (7).

L'absence de broncho-constriction, de laryngospasme, l'inhibition des secrétions trachéo-bronchiques facilitent la ventilation pulmonaire et aident, dans une certaine mesure, à éviter l'apparition de l'atélectasie pulmonaire post-opératoire. Le Fluothane peut être employé avec la chaux sodée. Il diminue le suintement capillaire et la perte sanguine per-opératoire. A l'instar des ganglioplégiques, il semble avoir un rôle antichoc. Il procure une certaine ataraxie post-opératoire. Au point de vue clinique, il semble non toxique: pas de fatigue, pas de troubles urinaires, pas d'anorexie.

Il est possible que le Fluothane se place au rang de l'éther et du cyclopropane. Il possède des qualités que ces derniers n'ont pas: non-inflammabilité, non-explosibilité, inhibition secrétoire trachéo-bronchique, antichoc, puissance, réversibilité rapide.

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CLINICAL OBSERVATIONS ON FLUOTHANE ANAESTHESIA*

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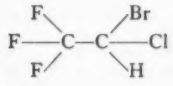
THE DEPARTMENT OF ANAESTHESIA at the Hôtel-Dieu Hospital in Quebec City has used Fluothane in many different types of anaesthetic machine with various techniques in a total of 1,112 surgical patients of all ages.

Fluothane is a volatile anaesthetic agent; it is a halogenated ethane, 2-bromo-2-chloro-1-1-1-trifluoroethane, with the structural formula:



PHYSICAL, CHEMICAL AND PHARMACOLOGICAL PROPERTIES

It is a clear, colourless liquid, with a specific odour. It is non-inflammable and non-explosive. It is a stable compound but theoretically, when exposed to air, moisture or light, it may in time break down into various acids of the halide group. The decomposition products may affect certain metals, such as tin and aluminum. Liquid Fluothane may attack rubber, producing softening and swelling. The rubber reverts to normal when withdrawn from the Fluothane. Clinically, the decomposition products have no toxic effects even though they are theoretically harmful. Thymol added to Fluothane, in a proportion of 0.01 per cent, protects Fluothane from the effects of light. Storage in a cool place, in amber-coloured bottles, also retards decomposition indefinitely. Fluothane is stable in contact with warm or cold soda lime, and it may be used safely in a closed circuit with a CO_2 absorber. On the skin, this anaesthetic does not produce the burning sensation which is felt after the application of ether or chloroform. It is non-irritating to the buccal, laryngeal or tracheal mucosa. It does not cause pulmonary oedema. Its therapeutic index is twice that of ether, and it is four times more potent. The anaesthetic ratio is from 1 to 3 per cent (1–3).

Table I shows the physical and chemical characteristics of Fluothane as compared with those of chloroform, ether, Vinethene, Vinamar and Fluoromar.

STATISTICAL DATA

In these studies, Fluothane has been administered using various types of anaesthetic apparatus: the Heidbrink No. 7 bottle with the wick atomizer, on

*Fluothane used in this study was provided by Ayerst, McKenna & Harrison Ltd., Montreal. Date sent for publication: April 27, 1957.

†Department of Anaesthesia, Hôtel-Dieu Hospital, Quebec City.

‡Doctors Laureat Jean, Jean-Louis Boivin, Pierre-Paul Paquet, Andre McClish, Jacques Pelletier and Egbert Daigle have contributed their help to this study on Fluothane.

Anaesthetic	Type	Chemical formula	Molecular weight	Boiling point	Specific gravity–liquid (water = 1)	Solubility in 100 parts water	Solubility oil–water 37° C.	Limits of flammability		Vapour tension at 20° C. mm. Hg
								Air	Oxygen	
Chloroform	Chlorinated hydrocarbon	$CH\,Cl_3$	119.39	61.26	1.49	0.822	100			160.5
Ether	Diethyl–ether	$(C_2H_5)_2O$	74.12	34.6	0.713	7.5	3.2	1.85–36.5	2.10–82.0	439
Vinethene	Divinyl-ether	$(C_2H_3)_2O$	70.9	28.3	0.774	4.0	41.3	1.7–27.0	1.85–85	-
Vinamar	Ethyl-vinyl-ether	$C_2H_5—O—C_2H_3$	72.10	35.8	0.759		45	—	2.1	4.85
Fluoramar	Fluorinated hydrocarbon	$CF_3—CH—O—CH—CH_2$	126.0	42.7	1.13	0.4	94	3.0	—	
Fluothane	Halogenated ethane	$CF_3—CH—Br—Cl$	197.39	50.2	1.86	0.345	330	Non-inflammable with O_2 0.5—50.0		243

inspiration and expiration; the Marrett and Boyle, in closed and semi-closed circuits; the McKesson, E.M.O., Friedman apparatuses; and the M.I.E. paediatric machine. The Fink valve was used for measuring pulmonary ventilation during anaesthesia.

Fluothane has been used alone with a nitrous oxide–oxygen mixture and in various other combinations.

Combined Anaesthetics

N_2O+O_2+Fluothane	817
Neraval$+N_2O+O_2+$Fluothane	92
Pentothal$+N_2O+O_2+$Fluothane	181
N_2O+O_2+Fluothane$+C_2H_6$	7
N_2O+O_2+Fluothane$+(C_2H_5)_2O$	4
Fluothane+local (knee)	1
Fluothane+brachial block	4
Fluothane+spinal	3
Fluothane+caudal	1
Fluothane+Viadril	2
	1,112

Fluothane has been employed in 1,112 surgical cases for different lengths of time, in patients of all ages and of both sexes (514 male, 598 female). Several patients were anaesthetized with Fluothane more than once, the intervals between anaesthesia varying from a few days to a few weeks (57 twice, 5 three times, and one four times).

Many patients received no pre-anaesthetic medication; for others, premedication did not differ from that currently used with other methods of general anaesthesia.

Preoperative clinical examinations demonstrated certain disease processes in some patients: pulmonary emphysema, pulmonary sclerosis, bronchitis, asthma, mitral stenosis, chronic endocarditis, coronary sclerosis, old infarct, bronchial obstruction, ventricular strain, diabetes, and vascular disorders of the extremities.

Clinical Studies

Studies of the effect of anaesthesia and of the action of Fluothane on the autonomic and central nervous systems, as well as on the cardio-respiratory and renal systems, give quite a clear concept of the clinical value of this new, volatile, anaesthetic agent.

Induction and Maintenance of Anaesthesia

Induction with Fluothane and nitrous oxide–oxygen (5:5 litres or 3:3 litres, according to the apparatus and the technique employed) should be slow and gradual rather than rapid, so that the concentration is kept within 1–3 per cent and adequate pulmonary ventilation maintained, while the pulse and blood pressure are kept under observation. Because a percentage-calibrated vaporizer was not available, an ether vaporizer bottle No. 7 with wicks was used in the Heidbrink machine. The control is opened gradually up to No. 4 and, for maintenance, it is turned back to Nos. 2 or 3. With both the Marrett and Boyle's

General Type of Surgery Involved

Ophthalmology	33
Otorhinolaryngology	467
General surgery	335
Gynaecology	95
Urology	64
Orthopaedics	118
	1,112

Ophthalmology

Corneal cauterization	2
Correction of strabismus	8
Retinopexy	2
Dilatation of lacrymal ducts	4
Ptosis of eyelids	3
Removal of chalazion	2
Dacryocystorhinostomy	1
Ocular tension	2
Resection of sclera	1
Enucleation	4
Cutting of synechiae (iris)	1
Discission of eye	1
Plastic surgery of orbit	2
	33

Otorhinolaryngology

T+A	324
Sinus washing	12
Paracentesis	13
Submucous resection	21
Plastic surgery of nose	9
Caldwell-Luc	9
Œsophagoscopy	11
Mastoidectomy	9
Fenestration	8
Bronchoscopy	5
Laryngoscopy	4
Radical frontal sinus operation	1
Suture tonsillar fossa	2
Plastic surgery of ear	4
Tracheotomy	3
Removal of mastoid packing	6
Removal of cerumen	2
Oro-pharyngeal abscess	7
Removal of salivary glands	3
Resection of œsophageal diverticulum	1
Bronchial aspiration	5
Dental extraction+filling	8
	467

General Surgery

Appendectomy	34
Cholecystectomy	23
Cholecystoduodenectomy	1
Inguinal hernia	20
Gastrectomy	8
Gastroenterostomy	2
Gastrotomy	2
Vagotomy	1
Artificial anus	4
Sigmoidectomy	3
Adhesions	1
Duodenojejunostomy	1
Intestinal resection	2
Hemicolectomy	2
Diverticulectomy	1
Abdomino-perineal	2
Biopsy of omentum	1
Partial hepatectomy	1
Resection of intestinal polyps	1
Closure artificial anus	1
Removal abdominal drainage	8
Umbilical herniotomy	6
Eventration	11
Removal superficial sutures	2
Crural herniotomy	1
Hæmorrhoidectomy	6
Abscess of anus	8
Rectoscopy	3
Mastectomy	20
Staphyloplasty	17
Thyroidectomy	13
Biopsy of breast	9
Abscess of breast	4
Stripping	8
Lumbar sympathectomy	2
Suprarenalectomy	1
Face wound repair	12
Removal skin tumour	10
Temporal abscess	2
Paronychiae	40
Anthrax	10
Lymphadenitis	9

General Surgery (continued)

Biopsy gland of neck	6
Radical excision of neck	5
Cyst of neck	1
Ligation occipital artery	1
Biopsy of tongue	2
Pilonidal cyst	2
Skin graft	5
	335

Gynaecology

Gynaecological examination and uterine curettage	47
Hysterectomy	29
Colpoperineorraphy	10
Wertheim	2
Vulvectomy	1
Oophorectomy	3
Bartholinian abscess	1
Cotte's operation	1
Salpingo-oophorectomy	1
	95

Urology

Cystostomy	3
Castration	1
Cystectomy	1
Inversion of tunica vaginalis (hydrocele repair)	3
Ureterosigmoidostomy	1
Prostatectomy	3
Nephrectomy	2
Pyelotomy	1
Pylography	1
Lumbotomy	1
Cystoscopy	23
Circumcision	24
	64

Orthopaedics

Bone marrow puncture	3
Bursectomy	5
Costotomy thoracic drainage	4
Open reduction	31
Club foot stretching of tendons	9
Finger repair	5
Torticollis	1
Resection of bone	12
Leg cast	9
Synovial cyst (wrist)	4
Dislocation of maxilla	1
Menisectomy of knee	7
Saucerisation of femur	1
Amputations	8
Removal Kirschner wire	5
Plaster corset	2
Laminectomy	1
Hallux valgus	1
Wound débridement	9
	118

Age

0–6 mo.	7
6 mo.–1 year	23
1–5	134
5–10	154
10–15	56
15–25	161
25–35	144
35–45	133
45–65	220
65–75	70
75–85	10
	1,112

Duration of Anaesthesia

0–30 minutes	246
30–45	378
45–60	128
1–2 hours	233
2–3	84
3–4	28
4–5	10
5–6	5
	1,112

machine, Fluothane is placed in the Trilene bottle, this is opened to approximately the same figures, the plunger in the Trilene bottle with the Boyle apparatus being completely withdrawn.

There seems to be no analgesic period. The second phase differs from that of ether, there being no mental confusion, delirium, tears, cries, coughing, sneezing, eructation, nausea, vomiting, salivary or tracheo-bronchial secretions or convulsions noted. Surgical anaesthesia resulted in four to eight minutes. Intubation could be done easily without producing coughing or bucking movements and, usually, without using a relaxant.

Premedication

None	111
Atropine only	16
Codeine+atropine	2
Morphine+atropine	417
Morphine+atropine+Benadryl	13
Morphine+atropine+Pacatal	6
Morphine+atropine+Stemetil	1
Demerol only	3
Demerol+atropine	459
Demerol+atropine+Benadryl	3
Levodromoran only	1
Levodromoran+atropine	16
Levodromoran+atropine+Benadryl	43
Levodromoran+atropine+Pacatal	20
Levodromoran+atropine+Sparine	1
	1,112

When Pentothal or Neraval is used, with or without relaxants, for the induction of anaesthesia, Fluothane should not be administered until the blood pressure has stabilized and the respiratory rate has become regular and adequate for proper inhalation of the anaesthetic.

On the basis of certain obvious anaesthetic signs, it would seem that Fluothane has some "ganglioplegic" activity. Whether or not the patient has received premedication, the pupils remain small and do not dilate progressively as they do during deep anaesthesia with ether. The conjunctivae become congested. There is absolutely no perspiration and salivary and tracheo-bronchial secretions are inhibited. The skin is warm and dry and the peripheral vaso-dilatation is present (4). There are no hiccoughs and no spasm of the larynx or of the bronchi. Stridor of the larynx has occurred in a non-intubated patient under deep anaesthesia for osteosynthesis of the tibia. When the concentration of the anaesthetic was reduced, this symptom disappeared. Fluothane did not produce

No intubation	377
Intubation with N_2O+O_2+Fluothane	486
Intubation with N_2O+O_2+Fluothane+ relaxant	249
	1,112

hiccoughs which sometimes occur during gastrectomy under anaesthesia with the thiobarbiturate–curare–nitrous oxide–oxygen combination.

Respiration

During induction and maintenance of anaesthesia with Fluothane, a decrease in depth or rate of respiration should be avoided. Whereas the rate and depth of respiration are likely to be depressed during induction, it is the depth which is most likely to become inadequate during maintenance. This respiratory depression may lead to hypoxia, CO_2 retention, cyanosis (due to inadequate ventilation rather than to broncho-constriction), and to cardiac irregularities. In our cases of fenestration, operations during which the surgical stimulus affects only slightly the rate of respiration, the minute volume was maintained at 4½ litres. This means that respiration must be assisted in many patients.

The depth of respiration should be watched closely and assisted respiration should be used with proper care. At the onset of anaesthesia, if respiration is assisted too forcibly, especially in children, this may cause an excessive concentration which is toxic to the heart. With Fluothane the heart appears to be saturated sooner than the brain, as it does with chloroform, and contrary to that which occurs with ether which saturates the brain first (6). Excessively prolonged assisted respiration or five to six movements of controlled respiration with a high concentration of Fluothane may produce a drop in blood pressure. Therefore, the concentration of Fluothane should be reduced during assisted or controlled respiration.

Bladder distension and certain surgical stimuli may cause tachypnoea, which is more apparent in young adults. The central respiratory reflexes do not seem to be abolished. Small doses of Demerol will relieve tachypnoea due to surgical stimuli. Assisted respiration is free and easy with Fluothane; resistance to assisted respiration was never present during induction, maintenance or recovery from anaesthesia.

Circulation

Fluothane has a characteristic action on the circulation. The pulse rate was often lowered to 70 or less. There was a 20 per cent decrease in blood pressure in the majority of patients. This hypotension is related to the degree of sympathicotonia present and to the depth of anaesthesia; however, it is reduced in intensity as anaethesia is prolonged, and thereafter the blood pressure remains only slightly below normal.

With Fluothane, vagal action on the heart predominates. This predominance increases the movement of the pacemaker and contributes to the occurrence of a nodal rhythm. Depression of the sino-auricular node may cause discharges from ectopic centres. These arrhythmias occur during rapid induction and during the deep stages of anaesthesia. They disappear if the concentration of Fluothane is decreased and ventilation hypoxia corrected, if present. These arrhythmias have occurred in 14 per cent of our electrocardiograms.

A vaporizer which gives a controlled concentration of Fluothane is therefore

not only useful but essential. The concentration should be limited to 3.5 per cent as a maximum (5). The following arrhythmias were found in our series of 1,112 patients: nodal, superior nodal, slight bradycardia, bigeminal and trigeminal pulse and extrasystoles of ventricular origin.

Our patients with old infarcts, cor-pulmonale and coronary artery disease did not appear to be adversely affected by the administration of Fluothane. Patients with emphysema accompanied by venous hypertension seemed to improve temporarily while under anaesthesia and for some time after.

ECG tracings were taken during prolonged anaesthesia with Fluothane, that is, during the fenestration operations.

A report on the "Summary of findings from 30 ECG's taken during anaesthesia with Fluothane," by Drs. Georges Saulnier and Jean Beaudoin, cardiologists in the Department of Medicine at Hôtel-Dieu Hospital, is presented here:

1. *Graphs taken preoperatively*
   - I. 21 strictly normal graphs.
   - II. 9 abnormal graphs, distributed as follows:
     - (*a*) 1 case sinus tachycardia rate 142.
     - (*b*) 1 case extrasystole.
     - (*c*) 1 case deeper *P* wave; possibly hypertrophy of right auricle.
     - (*d*) 6 cases non-specific changes of terminal phase, giving so-called "borderline" graphs.

2. *Graphs taken during surgery*
   - I. A moderate slowing of cardiac rhythm was found in most cases.
   - II. The abnormal graphs were not modified during anaesthesia.
   - III. Four electrical modifications are worthy of mention:
     - (*a*) Development of a nodal rhythm, 58/minute, 10 minutes after onset of anaesthesia. A graph taken 20 minutes after onset of anaesthesia shows that everything is back to normal (Fig. 1).

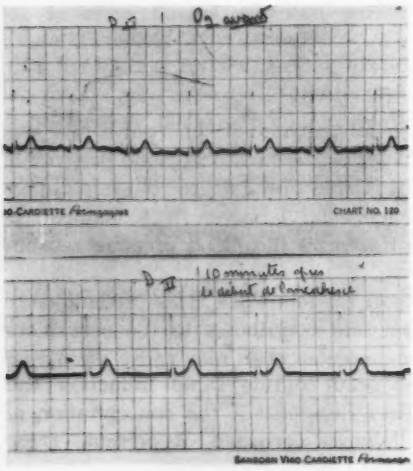


FIGURE 1

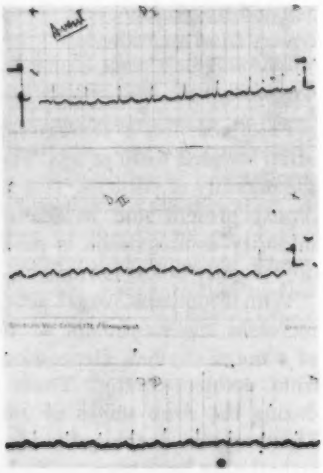


FIGURE 2

(*b*) Development of a bigeminal pulse 20 minutes after onset of anaesthesia; this is followed by the appearance of a coronary sinus rhythm which is still present 2 hours after the onset of anaesthesia (Figs. 2–4). Another graph taken 10 days after the operation shows that sinus rhythm is re-established.

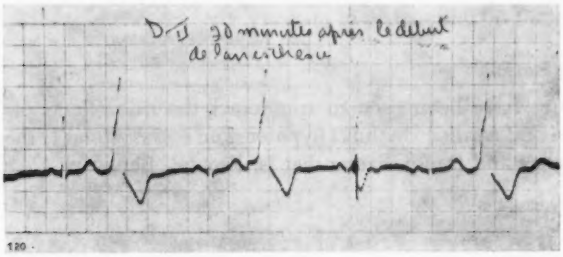


FIGURE 3

(*c*) A non-specific change in the terminal phase: flattened or inverted *T* waves in D^2, *AVL*, which started 2 hours and 45 minutes after the onset of anaesthesia and were still present 4 hours and 45 minutes after onset of anaesthesia (total duration of anaesthesia: 5 hours).

(*d*) In one patient, ventricular extrasystoles appeared 10 minutes after onset of anaesthesia.

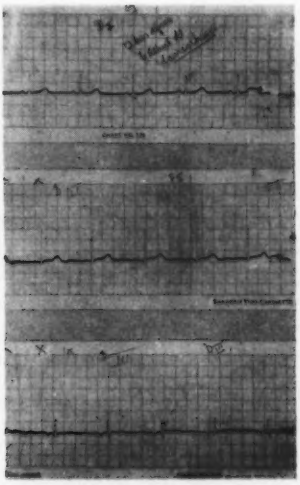


FIGURE 4

Flaxedil in small repeated doses produces more tachycardia than with other anaesthetics. Repeated does of Flaxedil have sometimes caused a tachycardia up to 150. Flaxedil does not cause hypotension as does tubo-curare; the blood pressure increases by 10–15 millimetres and the pulse rate is increased by 20 or more beats per minute, according to dosage. If hypotension should occur during maintenance of anaesthesia, it should be controlled by determining its possible causes. These may be high concentration of Fluothane, sudden haemorrhage,

traction on the bladder (distension), Fowler's position, and hyperventilation. Capillary oozing is markedly reduced, even after a three-hour period of anaesthesia with Fluothane. The use of adrenalin is dangerous and must be avoided during anaesthesia with Fluothane. Bladder distension may cause a blood pressure rise of 30–50 millimetres of mercury.

Adjuvant Medication

Various drugs have been used to counteract the side effects of Fluothane on the circulation and cardiac rhythm (hypotension, extrasystoles); these drugs were central vagolytics and tranquilizers, that is, Pacatal, Benadryl, Centrine, atropine and Demerol.

Supporting Medication	
None	905
Demerol	23
Atropine	38
Benadryl	78
Pacatal	55
Arfonad	4
Diparcol	3
Centrine	4
Benatrol	2
	1,112

With the exception of atropine and Benadryl given intravenously, which increased blood pressure and heart rate but did not entirely control pulse irregularities, adjuvant medication did not give the expected results. Demerol has decreased the respiratory rate; this depression is partly compensated for by an increase in depth but the compensation remains inadequate. Such medication is not an adequate substitute for proper anaesthetic technique. In some patients, pulse irregularities were controlled only by reducing the concentration or briefly stopping the administration of Fluothane.

Renal System

Experiments in rats have shown that renal function was not impaired by the repeated administration of Fluothane (2). In eight cases of fenestration, which were kept under Fluothane anaesthesia for approximately 4½ hours, urinalyses made on the day of the operation and on the third postoperative day have shown no sign of any pathological condition: that is, albumin, casts, or abnormal specific gravity.

Muscular Relaxation

Fluothane gives good muscular relaxation for lower abdominal operations. In upper abdominal operations, the relaxation obtained is not always satisfactory and, with Fluothane alone, adequate relaxation may occasionally be secured only at the cost of marked hypotension or cardiac arrhythmia. Twenty to forty milligrams of Flaxedil are usually needed; this dose changes pulmonary ventilation

very slightly or not at all, and it provides adequate relaxation without increasing concentration of Fluothane.

Relaxants	
None	837
Anectine	47
Anectine+syncurine	29
Brevidil	37
Brevidil+syncurine	20
Syncurine	2
Tubo curare	11
Flaxedil	129
	1,112

It is not always necessary to repeat this dose in closing the peritoneum. Experience should determine the proper administration of a relaxant, as required. Tubo-curare, which has "ganglioplegic" activity, is not recommended. Succinylcholine and decamethonium, having no hypotensive activity, are well suited to anaesthesia with Fluothane, with the understanding, however, that they should be used in small doses, either to increase muscular relaxation or to facilitate intubation.

Recovery

Consciousness returned from five to twenty minutes postoperatively. The patients awakened quietly; nausea was infrequent and might have been due to various other factors. The blood pressure remained exactly as if the patients had not been anaesthetized. The postoperative circulation was better than that observed after the use of other anaesthetics. This may be due to the fact that with other anaesthetics a depression in circulation follows the circulatory stimulation concurrent with anaesthesia, or it may be attributed to postoperative blood accumulation in the splanchnic area. On the other hand, with the use of Fluothane, there may be better circulation in the smaller blood vessels or the drug may have a superior action on the autonomic nervous system. There is no cyanosis of the extremities, no shivering or anything else which might resemble cyclo-shock. The blood pressure and peripheral circulation tend to remain normal; these facts support the statement that Fluothane has anti-shock activity (4).

If excessive muscular relaxation persists after the anaesthesia, and especially if 80 milligrams or more of Flaxedil have been used, 1 milligram of prostigmine and 0.4 milligram of atropine should be given, and while assisted respiration is maintained, Fluothane is eliminated.

Postoperative Period

It is our impression that postoperative pulmonary complications are less and that respiratory function in emphysema is improved in the beginning of anaesthesia. It is generally considered that the postoperative pulmonary complications which occur during the first few days have really started soon after awakening and may be due to the retention of respiratory secretions caused by the

anaesthetics, a muscarinic effect of the relaxants, the parasympathomimetic drugs, or painful reflexes. On the other hand, Fluothane depresses the cough and broncho-constrictor reflexes, even those generally induced by the induction of a laryngoscope or endotracheal tube. This beneficial effect is seen during bronchial aspiration carried out during Fluothane anaesthesia. Since salivary and tracheo-bronchial secretions are minimal with Fluothane, even without premedication, it is easy to understand that postoperative pulmonary atelectasis should be decreased. Our study of 1,112 cases would seem to substantiate this impression.

Ten patients, who had another type of anaesthetic a few days previously, had a bronchial aspiration under Fluothane anaesthesia. As soon as the aspiration was completed and the irritation caused by the catheter had subsided, the patients returned spontaneously to normal respiration; there was no cough, spasm, or any production of fresh secretions. This procedure, which completely oxygenates the patient before aspiration, facilitates the technique to such an extent that in our Department of Anaesthesia it is preferred to all other methods used previously, including trans-tracheal, thiobarbiturates, N_2O-O_2-C_3 H_6, and topical anaesthesia.

No postoperative mental depression occurred in our series of patients. Patients who had been anaesthetized twice for fenestrations, once with Pentothal–nitrous oxide–oxygen and once with nitrous oxide–oxygen–Fluothane, stated that with Fluothane they felt less depressed the next day. This reaction might indicate a lower degree of toxicity—a sympatheticotonic state which might explain the anti-shock effect and the improvement in pulmonary function.

Cardiac Arrest

Two cases of cardiac arrest occurred early in this series but, with the use of appropriate therapeutic measures, recovery was complete.

1. *Female patient, 40 years of age,* in a state of severe vagotonia, scheduled for radical mastectomy. Premedication: levo-dromoran 2 milligrams; atropine 0.4 milligram. Induction: Pentothal 250 milligrams, succinylcholine 60 milligrams. Intubation followed by controlled respiration with N_2O-O_2-Fluothane. The patient was placed in the reverse Trendelenburg position. Suddenly, the heart stopped beating. Four minutes later, cardiac massage was carried out through a thoracotomy. The heart had stopped in the diastolic phase. Heart beats were resumed with the first massage movements. Some indication of cortical irritation was present. Treatment consisted of hypertonic glucose solution, repeated stellar infiltrations, and plasma. Consciousness returned during the evening; mental alertness did not seem impaired, with the exception of some mental confusion of 24-hour duration, and loss of memory for recent events which returned in a few days.

Seven days later, the patient was operated on for radical mastectomy; the operation lasted two hours and was uneventful. Premedication: levo-dromoran 2 milligrams, atropine 0.4 milligram, Pacatal 25 milligrams. Supporting medication: Pacatal 50 milligrams, Benadryl 50 milligrams. Induction and maintenance: N_2O-O_2-Fluothane-succinylcholine 40 milligrams. Postoperative period, normal.

2. *Female patient, 10 years of age,* obese, presented for emergency appendectomy. Premedication: Demerol 50 milligrams, atropine 0.3 milligram. Induction: Pentothal 250 milligrams, succinylcholine 60 milligrams. Maintenance: intubation, N_2O-O_2-Fluothane under controlled respiration with hyperventilation. When the caecum was drawn out, the blood pressure which was 120/80 fell suddenly and the heart stopped beating. Since marked resistance to respiration was present, the anaesthetist had just given 0.2 milligram atropine

intravenously. Cardiac massage was carried out through a thoracotomy. Appendectomy was performed. No postoperative complications occurred. What is the explanation for this cardiac arrest? The dose of Pentothal was a factor, the succinylcholine used was a month old; there was a possible muscarinic effect; the resistance to ventilation may have been due to spasm or a muscarinic effect of the relaxant; controlled respiration with marked positive pressure decreasing venous return; some hypoxia due to broncho-constriction; an effect on the heart due to the high concentration of Fluothane; or, finally, a reflex action from traction on the caecum. All these factors may have contributed to the cardiac arrest, especially the controlled respiration combined with the high concentration of Fluothane. The heart was dilated and it was necessary for the surgeon to massage it ten times before cardiac action was re-established. No drugs were used.

Both these incidents occurred under the same conditions, with the use of the same drugs and the same anaesthetic machine; this machine was later inspected and its oxygen outlet was found defective. Therefore, there was an error in technique and this would have passed unnoticed with the use of another anaesthetic.

Since then, controlled respiration, especially with hyperventilation, has been abandoned in favour of assisted respiration, which is the only type employed at the present time. Use of relaxant agents has also been changed; our most current method is now to employ only small doses of Flaxedil.

Conclusions

Fluothane has been used for anaesthesia in 1,112 surgical cases. No fatalities have occurred either during surgery or during fifteen days after the operation.

Death occurred in three patients with cancer and in one with spinal trauma at a late postoperative date. Any reasonable connection with the anaesthetic can be disregarded.

1. *Male, 53 years of age.* Fracture of L1-L2, section of terminal cord, intestinal and bladder disorders.
   November 18, 1956. Laminectomy. Anaesthetics: Pentothal 325 mg., Flaxedil 60 mg., N_2O-O_2-Fluothane.
   December 3, 1956. 15 days later: bronchopneumonia.
   December 3–4, 1956. Bronchial aspiration.
   December 4, 1956. Patient died, 16 days after operation. Terminal bronchopneumonia.

2. *Male, 47 years of age.* Rectal neoplasm dating back to January, 1956.
   February 8, 1957. Artificial anus. Anaesthetics: N_2O-O_2-Fluothane, Flaxedil 20 mg.
   February 21, 1957. Second operation. Anaesthesia without Fluothane.
   March 5, 1957. Patient died, 25 days after anaesthesia with Fluothane. Generalized metastases.

3. *Female, 48 years of age.* Bladder neoplasm.
   November 28, 1956. Removal of bladder clots. Anaesthetic: N_2O-O_2-Fluothane.
   January 21, 1957. Patient died, 54 days after anaesthesia. Metastases.

4. *Male, 75 years of age.* Achromic melanoma.
   December 4, 1956. Cystostomy. Anaesthetics: Neraval 625 mg., N_2O-O_2-Fluothane.
   February 3, 1957. Patient died, 61 days after anaesthesia with Fluothane. Cerebral metastases.

The following conclusions may be drawn from this study of 1,112 cases of anaesthesia with Fluothane:

Fluothane has many advantages. Its disadvantages are easily controlled. It is a potent, volatile anaesthetic; its action is easily reversible; it is non-explosive and non-inflammable (it can even put out a flame). It produces smooth and easy induction, and is well tolerated by the patient. Induction should be slow, gradual and progressive. The patient should be maintained quietly without hyperventilation and without sudden increases in concentration; a properly calibrated vaporizer should be used. This is the best way to avoid a sudden hypotension, cardiac arrhythmias and respiratory depression which this anaesthetic may produce (7).

The fact that there is no broncho-constriction and no laryngospasm, and that tracheo-bronchial secretions are diminished, facilitates pulmonary ventilation and contributes somewhat to less postoperative pulmonary atelectasis. Fluothane may be used with soda lime. It decreases capillary oozing and blood loss during surgery. It appears to have anti-shock activity, in the manner of the "ganglioplegic" agents. It has a mild postoperative ataraxic effect. Clinically, it seems to be non-toxic; there are no urinary disorders, fatigue or anorexia.

Possibly Fluothane is the equal of ether and cyclopropane, but has advantages which are lacking in both these agents: non-explosibility, non-inflammability, inhibition of tracheo-bronchial secretions, anti-shock, potency, and easy reversibility.

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CLINICAL EVALUATION OF FLUOTHANE WITH SPECIAL REFERENCE TO A CONTROLLED PERCENTAGE VAPORIZER

IAIN M. MACKAY, M.D., F.A.C.A.*

EACH NEW DRUG which comes to the attention of the clinical investigator is destined to become the subject of controversy. The critical distrust displayed by some investigators is weighed against the over-enthusiasm of others. Each new contribution to the literature must therefore be accepted only tentatively and the conclusions drawn by the various clinicians must be carefully balanced one against another.

This paper presents a series of 203 cases of anaesthesia with 2 brom, 2 chlor, I,I,I, fluoro-ethane, which has become known as Fluothane and which will be referred to as such throughout this paper. This investigation has been carried out over the period from October 31, 1956, to May 1, 1957, and includes a full range of surgical procedures as well as obstetrical deliveries performed under this new anaesthetic agent, as shown in Table I.

TABLE I

Type of procedure or region involved	Number	Type of procedure or region involved	Number
Obstetrical: vaginal delivery	18	E.N.T.	
Inguinal	5	Mouth, throat, dental	12
Intrathoracic		Ear	5
Pulmonary and cardiovascular	10	Nose and sinuses	8
Thoraco-abdominal	1	Neck: major and minor	9
Upper abdominal		Peripheral nerves	3
Major	15	Perineal	
Minor	1	Genito-urinary	10
Peripheral vascular: arterial	4	Gastro-intestinal	4
Chest-wall: minor	2	Gynaecological	14
Spinal column		Intracranial	
Laminectomy	5	With hypothermia	4
Cervical or lumbo-sacral fusion	6	Without hypothermia	3
Lower abdominal:		Extremities	
Genito-urinary	4	Hip (S.P. Nailing or Moore Arthroplasty)	4
Gastro-intestinal	5	Other major orthopaedic	12
Gynaecological	6	Plastic and minor procedures	20
Eyes	13		

METHODS OF INVESTIGATION AND APPARATUS

In order to eliminate one of the most important sources of experimental error—that arising from differing interpretations of observed facts—all cases included in this series are those in which anaesthesia was personally administered by the author.

In this series, Fluothane was administered by several inhalational methods. In all except the open drop cases, oxygen has comprised 50 per cent or more of

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the vehicular gas mixture, the only other component of which has been nitrous oxide. Table II shows the type of circuit or the method used and the number of patients for which each was used.

TABLE II

Method	Number
Open drop on gauze mask	2
Closed, CO_2 absorption	10
Semi-closed, circle CO_2 absorption	23
Semi-closed, to-and-fro CO_2 absorption	9
Continuous flow (semi-open) non-rebreathing gas flow of 8 to 12 litres per minute.	159

Very limited experience of the open drop method shows it to be practical and possibly of value for mass casualty anaesthesia. The closed method with CO_2 absorption is not considered desirable, as one has no idea of the concentration of the drug in the circuit, and wide fluctuations of blood pressure and pulse occur. The semi-closed method with CO_2 absorption (circle or to-and-fro) allows greater control of the drug, and therefore provides much smoother anaesthesia; the higher the gas flow, the greater the ease of maintaining reasonable levels of blood pressure, pulse and respiration, but variations occur more frequently than is desirable.

In the author's opinion the continuous flow semi-open or non-rebreathing technique using gas flows of eight to twelve litres is the technique of choice for the administration of Fluothane. It allows maximal control of concentration and the greatest ease of control of blood pressure level, pulse and respiratory rate.

Since Fluothane is a volatile liquid it must be vaporized for use in anaesthesia. A number of vaporizing chambers have been investigated or devised. The types used in this series and the number of cases done with each are shown in Table III.

TABLE III

Type of vaporizing chamber	Number of cases
Ether vaporizer (Heidbrink)	
(*a*) wick removed	1
(*b*) wick above fluid level	27
(*c*) wick below fluid level	1
(*d*) wick replaced with tube above fluid level	8
Rowbotham Bottle	12
Trilene Vaporizer (B.O.C. Boyle's Type) with no special calibration	8
Fluotec (Cyprane) Vaporizer	144

Since most of the gas machines in use at the Toronto General Hospital are Heidbrink Machines of one type or other, the ether vaporizer of this equipment was the most readily available chamber for Fluothane. With the wick removed almost no Fluothane comes through the circuit. With the wick in place and approximately 40 ml. of Fluothane in the bottle a fair degree of control is

possible, but is not constant, owing to changes in fluid level and temperature. With the fluid level above the bottom of the wick, alarmingly high concentrations of Fluothane are obtained which are relatively uncontrollable. Replacing the wick with a tube extending down to a point near the fluid level provides control much like that obtained with the wick above the fluid level.

The Rowbotham Bottle with a non-rebreathing high flow method provides good control with adequate and apparently safe concentrations of Fluothane. The bottle must be refilled frequently.

The British Oxygen Company Boyle's T.C.E. vaporizer provides reasonable safety and control. However, because of changes in temperature and fluid level, the concentrations obtained vary greatly and the vaporizer requires constant adjustment.

The "Fluotec" (Cyprane) Vaporizer is a controlled percentage vaporizer manufactured in England. With the non-rebreathing technique it provides a most satisfactory and safe method for the administration of Fluothane. The degree of control achieved with this temperature compensated vaporizer is analagous to that provided by the flowmeter for cyclopropane and other gases. The "Fluotec" has been

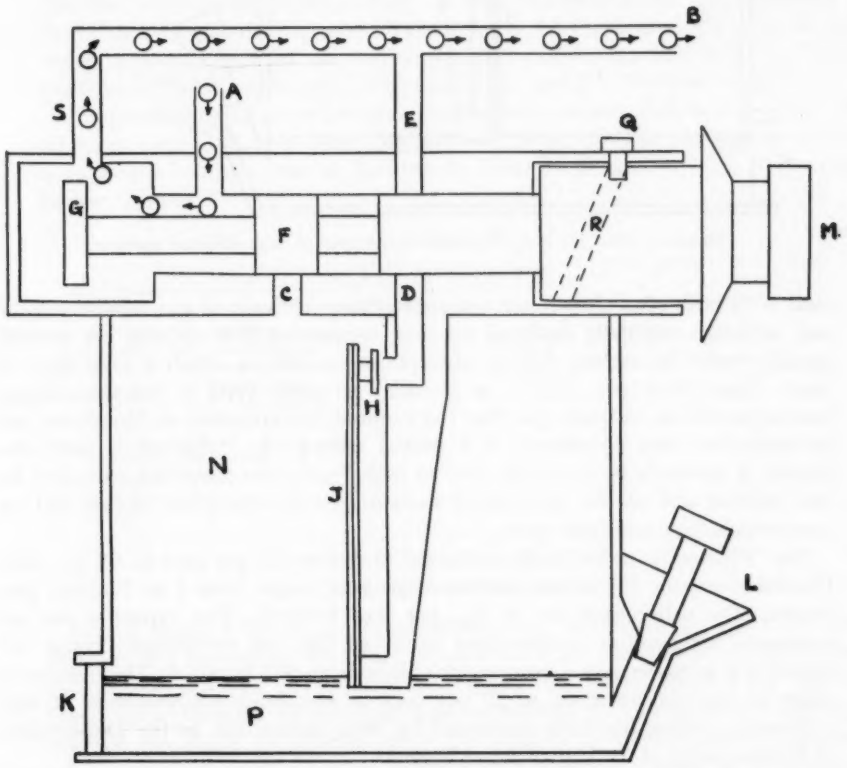

FIGURE 1. The "Fluotec" Vaporizer in the "off" position.

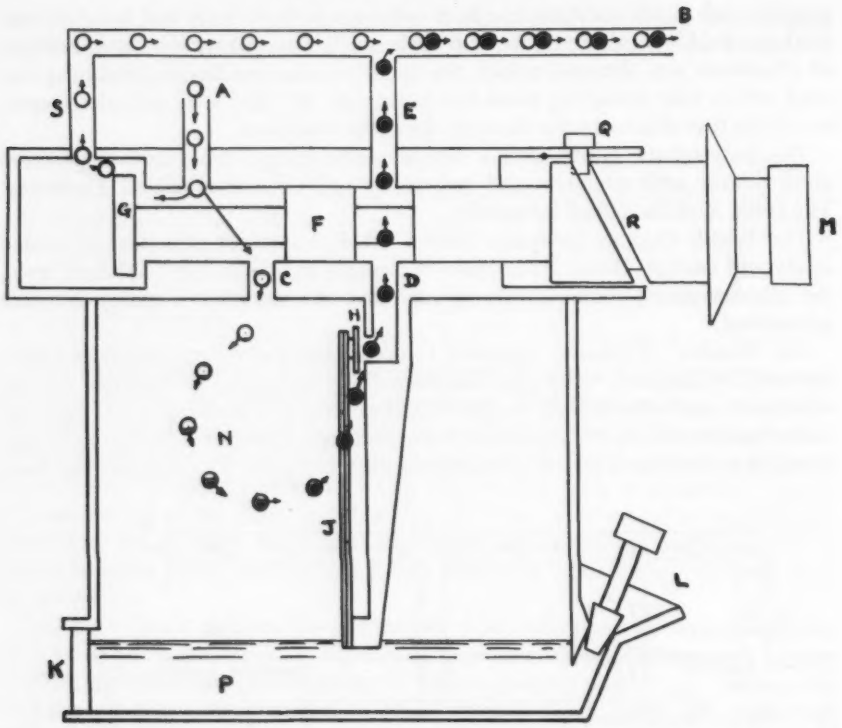

FIGURE 2. The "Fluotec" Vaporizer in the open or any calibrated position.

used with both semi-closed and non-rebreathing methods of gas administration and, although originally designed for only continuous flow circuits, has proved equally useful for carbon dioxide absorption methods in which a high flow of gases (four litres per minute or greater) is used. With a non-rebreathing technique and an adequate gas flow the inspired concentration of Fluothane can be controlled very accurately. If a partial rebreathing technique is used the degree of accuracy is, of course, not so high, but control may be exercised in this method and in the semi-closed carbon dioxide absorption circuit just as one controls the anaesthetic gases.

The "Fluotec" is individually calibrated to deliver 0.5 per cent to 3.0 per cent Fluothane vapour by volume, within a gas flow range from 4 to 16 litres per minute. The calibrations are at $\frac{1}{10}$ per cent intervals. The vaporizer has an automatic temperature compensated valve, so that the percentages being delivered are accurate over a temperature range from 55° to 90° F. The designer's claim of maximal variation of 20 per cent in Fluothane concentration at any calibration setting has been confirmed by tests carried out in the Department of Pharmacology at the University of Toronto.

Although this vaporizer is designed primarily to fit a Boyle's machine (B.O.C.

or M.I.E.) it can be readily adapted to any other make of machine. It is a heavy, accurately machined, completely closed and sealed piece of apparatus, with a clear glass level window, leak-proof filling funnel and drain plug (Fig. 3). Figures 1 and 2 will provide some idea of the mechanism of the "Fluotec." Figure 1 shows it in the "off" position. Figure 2 shows it in the open, or calibrated, position. Referring to Figure 1 (off), metered gas enters at A and as shown by the arrow it meets the spindle F, goes through the by-pass valve G, along the port S to B and thence to the patient. None of the gas can enter or leave the vaporizing chamber N as ports C and D are closed by spindle F. Rotation of the control M causes the spindle F to move to the right by virtue of the spiral groove R.

As the spindle F moves to the right the ports C and D are opened and the opening of the by-pass port G is considerably reduced. This results in the "open" position. In the "open" position (Fig. 2) metered gas enters at A and on reaching the spindle F divides, some going through the by-pass G as in the "off" position, and some going through port C into the vaporizing chamber N. Here the gas picks up "Fluothane" vapour and passes on through the valve H. Valve H is thermostatically adjusted by means of the bi-metallic strip J, so that the valve controls the outflow of the Fluothane-laden gas according to the temperature in the vaporizer. This rich gas, having passed the valve H, goes along to port D to E at the end of which it joins and mixes with the "clean" gas from S. The filling funnel is illustrated at L, and K is the level window.

Preoperative medication has been deliberately uncontrolled in this series, and all types were used as is shown in Table IV. Most of these patients were given a moderate bedtime dose of barbiturate (usually Seconal gr. $\frac{1}{1ss}$) the night before operation.

TABLE IV

Preoperative medication: drug or combination of drugs	Number of cases
Opiate with atropine	21
Opiate with scopolamine	7
Demerol with atropine	84
Demerol with scopolamine	38
Demerol with Phenergan	36
Atropine alone	8
Opiate alone	1
Opiate with barbiturate	1
Largactil with Demerol	1
Largactil, Demerol, Phenergan	1
Nil	5

Induction of Anaesthesia

In 174 patients induction of anaesthesia was performed by the intravenous injection of a thiobarbiturate in 2½ per cent solution. The common drug used was thiopentone although thioamylal was used in a few cases. The dose for induction varies from 100 mgm. to 450 mgm. with an average dose range of 150–250 mgm. For the remaining 29 patients either barbiturates or the intravenous approach were contraindicated: 27 were induced by Fluothane vapour in a mixture of

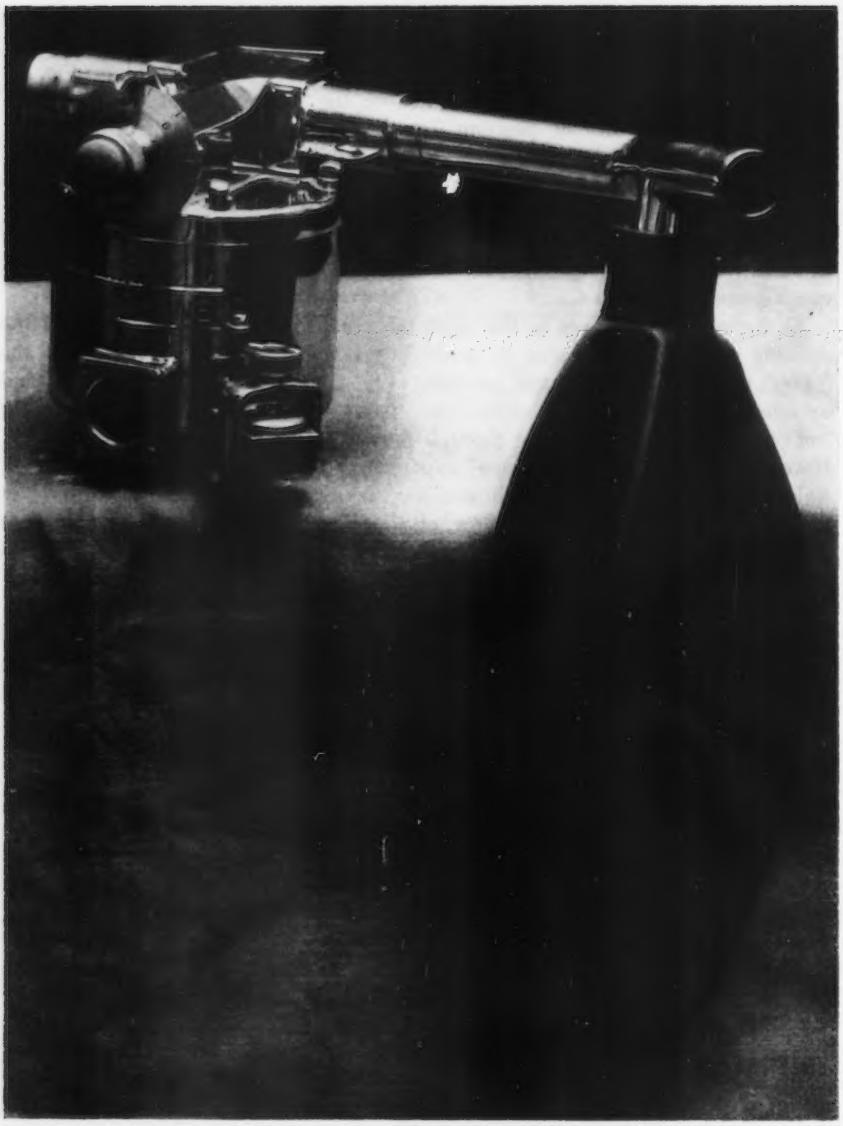

FIGURE 3. The "Fluotec" Calibrated Vaporizer for Fluothane.

nitrous oxide and oxygen in the 50/50 ratio; the remaining 2 by the open drop method.

Intubation, when performed, has usually been facilitated by the intravenous injection of 10–100 mgm. of succinylcholine chloride. For most patients the larynx has been sprayed before intubation with a topical anaesthetic agent. Occasionally neither spray nor relaxant has been used.

Ventilation with nitrous oxide and oxygen 50/50 has been carried out for all patients following intubation until spontaneous respirations have been re-established, before Fluothane has been introduced into the circuit.

Maintenance of Anaesthesia

Anaesthesia has been maintained with Fluothane in a vehicle of oxygen or a 50/50 mixture of nitrous oxide with oxygen.

Relaxant drugs have been used for 37 patients, after Fluothane was started or for purposes other than the facilitation of intubation. For 19 succinylcholine chloride has been used by continuous drip technique. For 6 it has been given intermittently. Gallamine has been given intermittently throughout operation to 10 patients. Only 2 received d-tubo-curarine as a relaxant. For both the dose used was small and no adverse effect was seen. Demerol has been given to 12 patients by intermittent intravenous injection as an adjunct to anaesthesia. No incompatible reaction has been observed. Largactil (chlorpromazine) has been used for two patients with hypothermia to control shivering in the rewarming period. In both sharp falls in blood pressure occurred at once and the procedure has now been abandoned.

Special Procedures

Continuous visual E.C.G. control has been available for 9 patients only. In 7 cases the Monaghan Respirometer (Bennett) has been used to observe the degree of respiratory depression accompanying muscle relaxation due to Fluothane. Arrangements have been completed for Fluothane estimations in blood samples and in spot gas samples. This work has been begun and will be reported at a later date.

Clinical Observations

This colourless, volatile liquid has a relatively pleasant odour which is somewhat confusing to most anaesthetists because of its marked similarity to that of both trichlorethylene and chloroform. The vapour appears to be non-irritating and even in concentrations up to 2.5 per cent is well tolerated by the conscious as well as the unconscious patient. I have seen no evidence of dermatitis caused by contact with the vapour in the concentrations used clinically.

Although laboratory experiment has shown that liquid Fluothane attacks rubber, plastics, stainless steel, aluminium and tin, I have seen no evidence as yet of deterioration of any of the equipment used for the administration of Fluothane anaesthesia. However, it is worthy of note that the "Fluotec" Controlled Percentage Vaporizer must not be inverted or tipped from the upright position as

the sealing cement and gaskets are quickly attacked by any liquid in the chamber. This happened to the first vaporizer used in this series. The manufacturers recommend draining of the Fluothane chamber when the "Fluotec" is not in use.

The type of preoperative medication seems to have had little effect on either induction or maintenance of anaesthesia in this series. The incidence of hypotension during anaesthesia and of vomiting both during and after anaesthesia bears no significant relationship to type of preoperative sedation.

Induction of anaesthesia has been performed easily and smoothly in most cases. The short stage of excitement which was noted with the open drop method and on induction with Fluothane, nitrous oxide and oxygen was not in evidence after induction with an intravenous barbiturate. The highest concentration necessary for induction of anaesthesia was 3.0 per cent for one neurosurgical hypothermia procedure. For other hypothermia cases 2.5 per cent was necessary. With children the highest concentration necessary was 2.0 per cent. When a barbiturate was used for induction the highest concentration of Fluothane required was usually 2.0 per cent. Occasionally 2.5 per cent was used for two or three minutes.

In all patients not requiring deep relaxation, anaesthesia was readily maintained with a concentration of 1.0 per cent or less. For many only 0.5 per cent of Fluothane was necessary. Except in those cases in which the relationship between relaxation of muscles and depth of respiration was being investigated, the relaxation necessary for surgery was obtained with the use of various intravenous relaxing agents. Succinylcholine drip, intermittent succinylcholine and gallamine seemed to be equally satisfactory. Curare given to two patients in small doses (less than 15 mgm. total) did not produce any ill effect, but the method was not continued in this series. In all patients for whom relaxant drugs were used respirations were assisted or controlled.

Extreme variation in blood pressure was the most striking and troublesome complication of Fluothane anaesthesia. Hypotension occurred in 56 patients. This is defined as a drop in systolic pressure to a level of 80 mm. of mercury or lower, or a drop of 60 mm. of mercury in a normally hypertensive patient. Statistically this tendency cannot be related to the type of preoperative medication, although it appeared to be slightly less frequent when Demerol and atropine had been used. In 44 of these patients the chief pressure drop occurred immediately after induction. In 12 the hypotension occurred later in the operation or the blood pressure fell gradually throughout the period of anaesthesia. In a few cases the blood pressure picture has been quite bizarre with high and low spiking—within normal limits however. The systolic blood pressure of 8 patients rose either slowly or sharply and remained elevated.

The initial fall in blood pressure is of great interest. In a minor degree it occurred in almost all patients induced with an intravenous barbiturate and it was rare in those induced with Fluothane. It would appear that the fall in blood pressure may be due to the barbiturate and that the Fluothane may merely have prevented the usual rapid recovery.

A fall in blood pressure was much less common in those patients for whom the non-rebreathing system and the "Fluotec" vaporizer were used than with any other apparatus or method. One patient however, anaesthetized with the "Fluotec"

for surgery under hypothermia, had been taking reserpine for some months until two days preoperatively. This patient's blood pressure was most difficult to control.

Blood pressure fall was most frequent with the closed CO_2 absorption system and in those patients in whom good relaxation was achieved with Fluothane alone.

Hypotension was effectively corrected in most patients with methedrine 10–20 mgm. given intravenously. In only one neurosurgical case was it necessary—after the patient had received Largactil—to give norepinephrine by intravenous drip.

The pulse rate appeared in this series to be far from consistent. Although when a profound blood pressure fall occurred the pulse rate seemed to parallel it more or less closely; yet a rapid rise in pulse rate, apparently unconnected with carbon dioxide retention, was quite common.

The respiratory rate, although occasionally depressed to 16 per minute, showed a general tendency to rise to a level of about 30 per minute and frequently higher. The depth of respiration became much less as the rate was elevated. Measurements with the Monaghan Respirometer indicated that when fair abdominal relaxation was achieved the tidal volume was reduced to a very low figure, and that although the rate rose to 60 per minute the minute volume was only 6 litres.

One very interesting observation was made during intrathoracic procedures. With Fluothane anaesthesia control of respirations may very often be achieved and maintained merely by replacing the patient's spontaneous effort. Using a concentration of Fluothane of 0.7 per cent or less and without the use of relaxing agents, a quiet field may be provided for the surgeon. Most of these patients were given minimal unit doses (10–20 mgm.) of Demerol to aid the effect but the Demerol could probably have been dispensed with.

In spite of theoretical objections adrenaline has been given in a local anaesthetic drug by infiltration to several patients under Fluothane. There has been no adverse effect. Atropine given during Fluothane anaesthesia raises a depressed blood pressure if the pulse rate has also been depressed.

Cardiac irregularities have been observed in six patients. Three cases were cardiac surgical procedures. One was a neurosurgical hypothermia in which a tight brain was probably responsible. In this case apnoea also occurred at the same time. The introduction of a brain needle corrected both phenomena but the operation was terminated and on rewarming the patient appeared quite normal.

Vomiting has occurred infrequently in this series. Four patients vomited during anaesthesia, three of them regurgitating around a duodenal tube when the surgeon squeezed the stomach. Six patients vomited once during the immediate postoperative period. One other patient is known to have vomited during the twelve hours following anaesthesia, and others may have done so without our knowledge. A small number of patients complained of mild nausea on waking but did not vomit.

Salivary secretions have been troublesome in only four patients at the end of operation.

One of the most striking observations has been the short waking period following Fluothane anaesthesia, and the rapid return of mental orientation. This has often been immediate and all patients of the series seem to have been alert within 30 minutes of the end of the procedure.

Postoperative analgesia has been poor and the patients require sedation very soon.

In the eighteen vaginal deliveries performed under Fluothane it was noted that nine patients showed evidence of uterine relaxation to a troublesome degree. Decrease in Fluothane concentration seemed to correct this. There was no observable effect on the baby in any of these cases.

One death has occurred in this series. One neurosurgical patient operated on under Fluothane and hypothermia bled twelve hours postoperatively, possibly owing to Largactil given in the warming period, and died four days postoperatively.

Conclusions

Fluothane is a very potent anaesthetic agent and should be administered with care, as minor variations in concentration may produce profound effects. It is probably inadvisable to give Fluothane by the closed CO_2 absorption technique and the most satisfactory and the safest method at present available appears to be the non-rebreathing continuous flow circuit (nitrous oxide and oxygen) with the "Fluotec" temperature compensated vaporizer.

Type of preoperative medication has little, if any, influence on the course of Fluothane anaesthesia.

Succinylcholine and gallamine may be quite safely used with Fluothane.

Abdominal relaxation cannot be achieved with Fluothane alone without producing a marked respiratory depression.

A fair degree of respiratory control for intrathoracic surgery can be achieved with Fluothane.

The most favourable characteristics of Fluothane appear to be potency, acceptability to the patient, a rapid waking period and relative freedom from postoperative side effects.

Acknowledgments

The author is indebted to Ayerst, McKenna and Harrison Co. of Canada for the generous supplies of Fluothane made available for this investigation, to Mr. Fraser Sweatman for the loan of a "Fluotec" Calibrated Vaporizer and to Dr. Werner Kalow of the Department of Pharmacology, University of Toronto, for checking the vaporizer's calibrations and for his continuing co-operation.

Summary

A series of 203 surgical and obstetrical patients anaesthetized with Fluothane at the Toronto General Hospital is presented. The methods and technique used and special apparatus available are discussed and clinical observations are given in detail.

Résumé

Dans le but d'apprécier les effets du nouvel anesthésique liquide volatil Fluothane, nous avons fait, à l'hôpital Toronto General, des épreuves cliniques.

Nous présentons deux cents cas. Tous les patients ont été anesthésiés par l'investigateur lui-même.

Les méthodes d'administration employées ont été le goutte à goutte, le semi-fermé avec absorption du gaz carbonique, le circuit fermé avec absorption du gaz carbonique et le flot continu sans réinspiration. Nous avons aussi employé les techniques de pression positive et négative dans quelques cas de thorax ouvert.

Cette substance a été évaporée dans des appareils variés dont la bouteille à éther Heidbrink, la bouteille Rowbotham, la bouteille "Trilène" des machines Boyle et Marrett. L'appareil le plus utile a été le vaporisateur à pourcentage contrôlé Cyprane (Fluotec). Nous avons employé ce vaporisateur, possédant une grande précision et un système compensateur pour la température et la vitesse du courant gazeux, aussi bien en semi-fermé qu'en flot continu et, cela, avec d'excellents résultats. Avec ce vaporisateur, le flot continu constitue la méthode de choix pour l'administration du Fluothane.

Nous avons, dans notre série de cas, tous les types de chirurgie majeure et mineure. Nous avons employé l'appareil Cyprane pour 145 de ces cas.

Nos observations nous permettent de dire que ce médicament peut être à la fois utile et dangereux. Les avantages les plus transcendants du Fluothane sont: qu'il n'est pas inflammable ni explosif et il permet une induction agréable et un réveil rapide. La faible incidence des vomissements post-opératoires est surprenante.

Ses pires inconvénients sont: une tendance à produire de l'hypotension et à avoir des effets imprévisibles sur les systèmes respiratoire et cardiovasculaire. L'effet hypotenseur est difficile à exploiter car il s'accompagne d'un suintement sanguin marqué dans le champ opératoire.

Selon toute apparence, l'évaporation du médicament sur l'appareillage est sans conséquence.

Ce médicament constitute une addition à notre armamentarium. Il ne remplacera pas l'éther mais il pourra jouer un rôle important.

EVALUATION OF FLUOTHANE FOR CLINICAL ANAESTHESIA

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Pharmacological developments are unfolding so rapidly in the realm of anaesthesia that almost every week a new drug is made available for study and trial. With the increasing use of the cautery and the concerted effort to avoid explosions, a marked need has arisen for a safe, potent, non-inflammable inhalation anaesthetic drug. Robbins (1) in 1946 investigated a number of non-explosive fluorinated hydrocarbons in the laboratory and concluded that six might be of clinical value. No further work was done until 1953, when Krantz *et al.* (2) reported on the safety of a fluorinated ethyl vinyl ether. Unfortunately, this compound was explosive in anaesthetic concentrations (3). Meanwhile, Suckling in England, while screening non-explosive fluoride compounds, synthesized 2 bromo-2 chloro-l,l,l, trifluoroethane ($CF_3CHClBr$). This compound, called Fluothane, was investigated pharmacologically by Raventos (4), who found it to be a potent and safe anaesthetic drug in several species of animals. Within the last year several clinical reports attesting to the value of this drug have been published (5, 6, 7, 8).

Fluothane is a clear, colourless liquid with a sweet, pleasant odour resembling trichlorethylene or chloroform (Table I). The boiling point (50.2°C.) renders

TABLE I

Physical Properties of Fluothane

Appearance	Colourless, clear
Odour	Sweet, pleasant
Molecular weight	197.39
Boiling point	50.2° C.
Specific gravity	1.862 at 22° C.
Oil/water solubility	330.
Vapour pressure	243 mm. at 20° C.

vaporization by the open drop technique feasible and practical. The compound is non-inflammable and non-explosive in any concentration with air or oxygen. Although decomposed slowly by light to hydrochloric acid and phosgene, the drug is stable at room temperatures when treated with thymol, 0.01 per cent, and kept in light-resistant containers. It does not form toxic products with soda-lime in the presence of heat and can be used safely with the carbon dioxide absorption technique.

Laboratory Findings

Fluothane came to our attention in February, 1956.† Preliminary laboratory investigations in dogs and monkeys (9) confirmed many of the findings of

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†We are most grateful to Dr. John Jewell and Ayerst Laboratories, New York, for aid and encouragement in this project.

Raventos (4). The drug was extremely potent. It could produce severe respiratory depression and marked hypotension in three to five minutes when administered rapidly. However, respiratory paralysis due to over-dosage always preceded cardiac arrest. Fluothane did sensitize the myocardial conduction mechanism to epinephrine-like compounds, but peripherally acting vasopressors like methoxamine and neosynephrine could be injected safely with normal responses. The administration of d-tubo curarine chloride to a dog anaesthetized with Fluothane resulted in profound cardiovascular collapse, and yet succinylcholine could be injected with the anticipated normal effect. Chronic administration of Fluothane to seven dogs and two monkeys for 24 hours over a period of six days showed no advanced histological changes in any organs. In several of these animals there was some pallor of the hematoxylin-eosin stain in the areas surrounding the central vein of the liver lobules. This finding indicated that close attention would have to be directed to the effect of this drug on liver function. Such work is in progress at the moment.

Clinical Investigation

Fortified with the above laboratory data, staff and resident physicians administered Fluothane to 500 patients, varying in age from 8 months to 73 years (Table II). Although 63 per cent of patients were judged to be in good physical

TABLE II

Age Distribution of Patients Receiving Fluothane

Age (years)	Number of patients	Per cent
Less than 10	43	8.6
11–20	35	7.0
21–30	104	20.8
31–40	139	27.8
41–50	97	19.4
51–60	45	9.0
Over 60	37	7.4

condition, the drug has been employed successfully in patients with asthma, pulmonary emphysema, diabetes, moderate hypertension, arteriosclerotic heart disease and advanced carcinoma. Forty-three patients were considered to be poor risks. All types of surgical procedures (Table III) lasting from 10 minutes to 8½ hours (Table IV) have been included in the series.

TABLE III

Variety of Operations Performed with Fluothane

Operative site	Number of patients	Per cent
Head and neck	114	22.8
Trunk and extremities	193	38.6
Intrathoracic	53	10.6
Intra-abdominal	99	19.4
Perineum	39	7.8
Cancelled	2	0.4
Major operations	265	53.0
Minor operations	235	47.0

TABLE IV

DURATION OF ANAESTHESIA TIME WITH FLUOTHANE

Duration of anaesthesia	Number of patients	Per cent
Less than 1 hour	107	21.4
Less than 2 hours	157	31.4
Less than 3 hours	74	14.8
More than 3 hours	162	32.4

The premedication normally ordered was not changed drastically for patients receiving Fluothane. A short-acting barbiturate two hours preoperatively, followed by a narcotic (meperidine or morphine) one hour before operation, along with an anticholinergic drug shortly before induction, was the rule. It was noted that marked respiratory depression during anaesthesia was more prone to occur in patients who manifested a profound reaction to narcotics. The situation was similar to that which is seen with cyclopropane anaesthesia.

Atropine, 0.6 mg., and Antrenyl®, 0.6 mg., were believed to be important premedicant drugs, as they tended to minimize the incidence of bradycardia during operation.

Induction

Induction by the open drop technique was performed in 27 children. The vapours were accepted readily, but a short excitement period lasting about one minute usually occurred. Coughing, vomiting and laryngospasm were noticeably absent. The third stage was achieved rapidly in two to five minutes with Fluothane dropping at a rate of 30 to 40 drops per minute. With added oxygen flowing under the mask, eight children were maintained for two to three hours on 10 to 12 drops per minute for orthopaedic and plastic procedures. Other children were maintained with an endotracheal non-rebreathing valve technique or with the non-rebreathing mask. Hypotension and bradycardia have not been noted in children. Deep planes of anaesthesia were signified by progressive intercostal paresis.

In 86 (17 per cent) of the patients induction was achieved in a semi-closed circle absorption system, employing a four litre per minute flow of oxygen or two litres each of nitrous oxide and oxygen to vaporize Fluothane in a concentration of 3.5 to 4.0 volumes per cent. A short but intense excitement period was seen in the majority of these patients, but could be circumvented by administering a sleeping dose of an ultra-short-acting barbiturate (surital sodium, 75–200 mg.) prior to application of the mask. The majority of patients in this series (382) received this latter method of induction. In order of preference, Fluothane was vaporized from a Boyle "Trilene" bottle, a Foregger "vinethene" bottle, a Foregger "copper kettle" and a standard Heidbrink ether bottle with wick in place. All but the latter vaporizer were calibrated for flows of 4 litres per minute.

The rapidity of induction, associated with the early obtundation of pharyngeal and laryngeal reflexes, the masseter muscle relaxation and the absence of salivary secretions were remarkable in all patients. An oral pharyngeal airway

could be inserted in two to three minutes and endotracheal intubation accomplished, if performed with dexterity, in four to six minutes, without cessation of spontaneous respirations. The limitation to atraumatic, smooth intubation lay primarily in the rapidity with which anaesthesia lightened during the technical insertion of the tube. In 45 to 60 seconds the patient could be phonating and gagging. However, vomiting occurred during induction in only two patients. This reaction seldom provoked a laryngospasm and, on application of the mask, deeper planes of anaesthesia were obtained rapidly. Endotracheal intubation was employed in 276 (55 per cent) of patients. Of this group, 54 per cent were intubated with Fluothane alone. In the remainder, because of the above limitations, succinylcholine, 20 to 60 mg., was employed to facilitate insertion of the tube. Resumption of spontaneous respiration after the succinylcholine apnoea occurred smoothly and within the anticipated time period.

The signs of deepening anaesthesia were related primarily to the respiratory and cardiovascular systems. The classical signs of intercostal paresis and paralysis were similar to those seen with ethyl ether, except that with Fluothane they occurred much more rapidly. Respiratory paralysis due to Fluothane was seen rarely and easily reversed by lightening the plane of anaesthesia.

Developing hypotension was also considered to be a sign of increasing depth of anaesthesia and usually could be reversed by reducing the concentration of Fluothane. Since blood pressure is an important clinical reflection of cardiovascular function, careful attention was devoted to the incidence of hypotension with Fluothane. During induction significant fall in blood pressure occurred in 41 per cent of the patients (Table V). Figure 1(*a*) shows the anaesthetic record

TABLE V

DEGREE OF SIGNIFICANT HYPOTENSION DURING INDUCTION WITH FLUOTHANE

B.P. fall (mm. Hg)	Number of patients	Per cent
20–30	87	19.0
30–40	55	11.3
40–50	27	5.5
50–60	16	3.2
More than 60	10	2.0
Total	195	41.0

of a 55-year-old patient undergoing a thoracotomy and illustrates the typical hypotensive phenomenon. The prior adminstration of an ultra-short-acting barbiturate did not influence the incidence of hypotension. In all but sixteen patients the blood pressure returned to satisfactory levels with a lightening of the plane of anaesthesia, or associated with operative manipulation. Ancillary measures were judged necessary for the sixteen patients: Antrenyl® was administered to eight; vasopressor drugs to five; and for three Fluothane was discontinued temporarily. The exact cause of this hypotension is unknown, but it is interesting that patients receiving Fluothane had warm, dry extremities with full pulses and dilated veins, similar to what is seen following administration of chlorpromazine. This peripheral vaso-dilatation appeared to be a constant phenomenon.

Bradycardia was not common during induction. Only fourteen patients showed

a decrease in pulse rate of more than twenty per minute. The insistence on adequate doses of anticholinergic drugs given shortly before induction may account for this finding, which is somewhat dissimilar to that noted by others (8). Tachycardia was a rare occurrence.

Maintenance

In practically all adults, anaesthesia was maintained with equal flows of nitrous oxide and oxygen, at a rate of 4 litres per minute, as outlined above. This semi-closed technique was chosen arbitrarily and in an effort to maintain constancy of some factors during the evaluation. Satisfactory anaesthesia for most operations could be attained with a concentration of 0.8 to 1.5 volumes per cent of Fluothane being delivered from the vaporizer. The only supplementary drug employed in this series was succinylcholine. It was considered a useful adjunct to provide needed relaxation for upper abdominal surgery and to obtund or prevent bucking associated with hilar manipulation during intrathoracic procedures. Fluothane itself provided sufficient relaxation for other surgical operations.

As a rule surgical stimulation could be tolerated within three to eight minutes

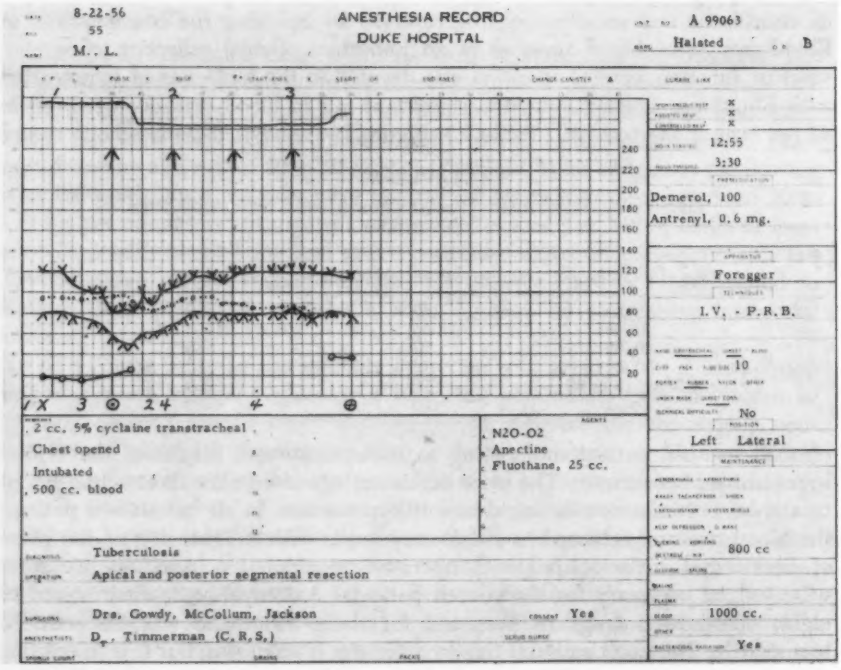

FIGURE 1(*a*) Anaesthetic record of 55-year-old male undergoing apical and posterior segmental resection of lung for tuberculosis. Anaesthetic drugs: surital sodium, 140 mg., cyclaine, 2.0 cc. 5% solution transtracheal, nitrous oxide, 2 litres, oxygen, 2 litres, Fluothane, succinylcholine, 200 mg.

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Thoracotomy for Pulmonary Tuberculosis

Surital, 140 mg., N_2O-O_2, Fluothane, Anectine, 200 mg.

Time	pH	pCO_2	O_2 Sat. %	
12:30	7.47	32.8	96	Control awake
1:35	7.40	38.8	100	Spon. resp. B.P. 82/50
2:30	7.61	19.6	100	Cont. resp. 45 mins.
3:10	7.51	28.2	100	Cont. resp. Closing
3:40	7.44	39.6	100	Tube out Coughing

FIGURE 1(*b*) pH, pCO_2 and oxygen saturation before, during and at conclusion of thoracotomy. Respirations controlled while in chest.

of beginning anaesthesia. The plane of anaesthesia could be altered with three or four respirations and fineness of control was limited only by the inadequacies of the vaporizers employed. The potency of the drug could be both a bane and a blessing. Rapidity and ease of control was offset by ease of over-dosage.

"Surgical" anaesthesia in this series was associated with depression of respiratory rate and depth, but particularly the latter. "Assisted" respirations were employed in nearly all cases. It was interesting to note in many patients how easily complete control of respirations could be assumed when assistance was begun. In this way the drug resembled cyclopropane. The anaesthesiologist had to watch the patient closely when controlled respirations were first instituted, because an increased depth of anaesthesia often developed in rapid fashion. Figure 1(*b*) shows that a tendency to alkalosis occurred when controlled respirations were employed. As with any other anaesthetic drug, if adequate alveolar ventilation was maintained, one did not need to fear respiratory acidosis with Fluothane.

In the majority of patients, as illustrated in Figure 1(*a*), hypotension at the

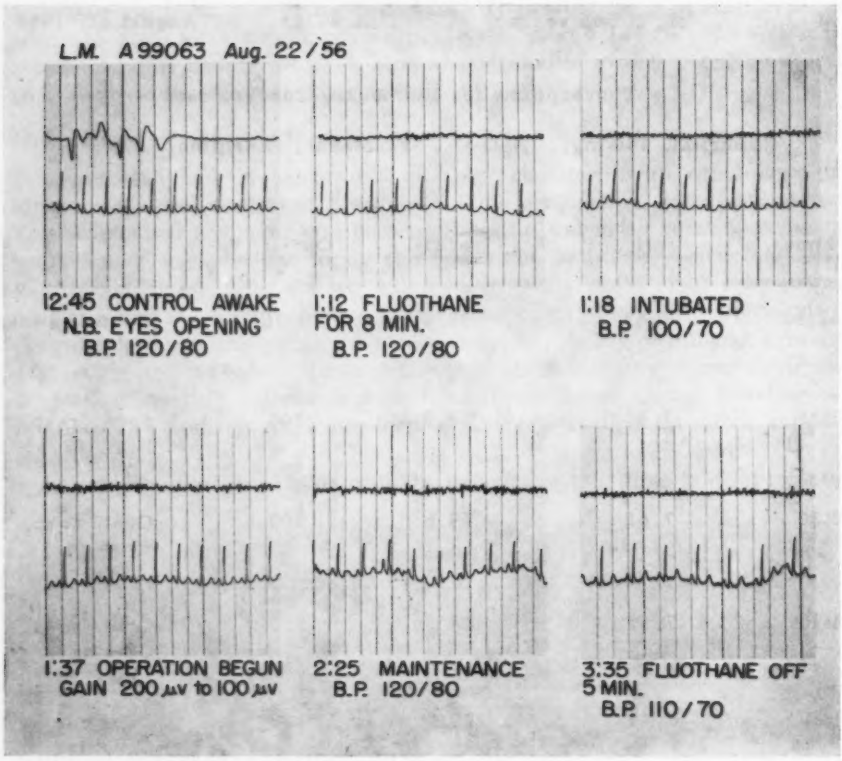

FIGURE 1(*c*) Electroencephalographic and electrocardiographic tracings recorded during operation on Edin anesthograph.

time of induction was corrected, usually spontaneously, during the maintenance period. However, in fifty-six patients (11.5 per cent) of this series a blood pressure fall of 20 mm. Hg or more occurred during operation. In ten patients unreplaced blood loss was judged to be the cause of the drop. Patients anaesthetized with Fluothane appear to be unusually sensitive to bleeding; in this way they resemble patients rendered hypotensive by ganglionic-blocking drugs. This observation reflects the peripheral vaso-dilatation seen clinically. In several patients the hypotension was associated with traction on the upper abdominal contents. This reflex appears to be initiated more frequently with Fluothane than with other drugs. The hypotension encountered required specific pharmacologic therapy in eleven patients. In the remainder the situation was corrected with transfusion or watchful waiting.

Bradycardia was not a problem during maintenance of anaesthesia. In only three patients did the pulse rate fall below 60 per minute.

With a halogenated compound like Fluothane, the possibility of cardiac arrhythmias is very real. In view of that fact that the injection of epinephrine

in the dog anaesthetized with Fluothane could produce ventricular fibrillation, we have avoided this combination. However, epinephrine for subcutaneous haemostasis was injected on four occasions inadvertently in this series, with no resultant clinical arrhythmias.

Continuous electrocardiograms were recorded in thirty patients early in the series. In eighteen patients no changes were seen. Seven developed nodal rhythm, three showed premature auricular contractions and two premature ventricular contractions. Clinical observation in the remainder of the series detected six arrhythmias of ventricular origin. All arrhythmias reverted spontaneously with lightening of the plane of anaesthesia or with improved ventilation. In no patient was it necessary to discontinue the drug administration. Arrhythmias have been noted less frequently as dexterity in administering the drug has improved. Preoperative arrhythmias have not become more serious under Fluothane anaesthesia.

The electroencephalogram was monitored in a number of patients (Figs. 1, 2). With increasing depth of anaesthesia fast activity disappeared and slow, high voltage waves became prominent. A pattern corresponding to Level 3 appeared to provide satisfactory anaesthesia.

Halogenated compounds are particularly prone to disturb liver metabolism or to produce irreversible cellular changes in this vital organ. Unfortunately, none of the laboratory tests available reflects in a convincing or complete manner the true status of liver function. Considerable cellular dysfunction or damage may be present without any objective evidence.

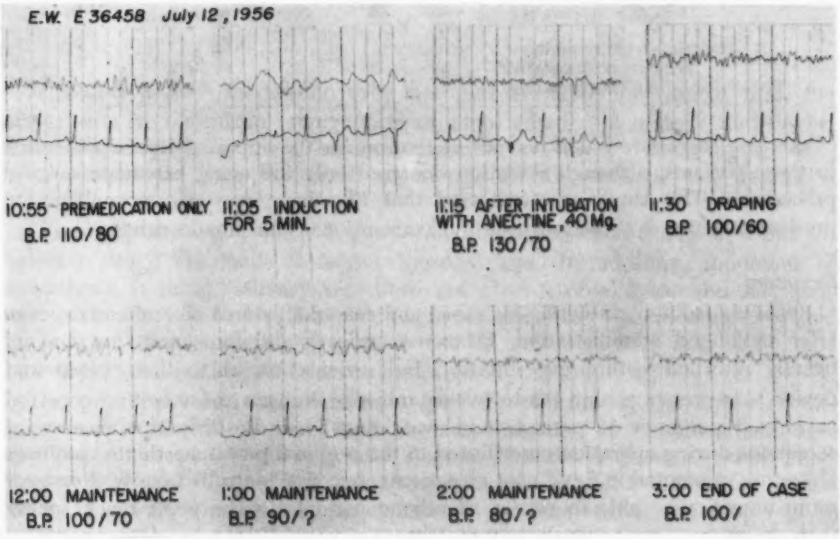

FIGURE 2. Electroencephalographic and electrocardiographic tracing of patient receiving fluothane anaesthesia. N.B. ventricular arrhythmias during induction period, rapid alteration in electroencephalographic patterns.

Recognizing the limitations involved, an attempt was made to assess the influence of Fluothane on liver metabolism. In twenty patients subjected to anaesthesia for two hours or more, blood sugar determinations were made pre-operatively, after one hour of anaesthesia, two to three hours after anaesthesia, and twenty-four hours postoperatively. The respective average blood sugar levels in mg. per cent were 106, 104, 111, and 95. In this group Fluothane produced less disturbance in blood sugar levels than most conventional anaesthetic drugs. These results may be a reflection on liver metabolism itself or an indication that stimulation of the adrenal medulla does not accompany administration of this drug.

Of the several liver function tests, the rate of clearance of bromsulphalein dye from the blood stream is as representative as any. In 51 patients who received Fluothane for more than one hour, BSP dye tests were performed 24 hours and 5 days following anaesthesia. Controls consisted of a similar group of patients subjected for more than one hour to ethyl ether, cyclopropane or pentothal, nitrous oxide, meperidine anaesthesia. The results are tabulated in Table VI. Abnormal dye retention was found in both groups. Careful analysis

TABLE VI

LIVER FUNCTION (BROMSULPHALEIN DYE RETENTION)

More than 5% retention in 45 minutes	Number of patients	Per cent
CONTROLS (51 patients)		
24 hours postoperative	22	43.1
5 days postoperative	7	13.7
FLUOTHANE (51 patients)		
24 hours postoperative	20	39.2
5 days postoperative	6	11.8

of the case reports revealed no specific reasons for the apparent liver dysfunction in these patients, although retention occurred only following extensive surgical procedures. This single test indicated that Fluothane was not more likely to produce hepatic dysfunction than the conventional anaesthetic drugs.

Recovery

Recovery from anaesthesia was rapid and remarkably free of excitement, even after prolonged administration. Protective reflexes and movement on demand usually returned within five minutes. Full orientation as to time, place and person was present within ten to twenty minutes. Nausea and vomiting occurred in only 6 per cent of patients and was short-lived. Possibly the absence of secretions during operation contributed to the minimal post-anaesthetic vomiting. Shivering was noted in 5 per cent of patients, but was controlled easily. Recovery room nurses were able to return Fluothane patients to the ward much sooner than others.

Postoperative morbidity was minimal in this series. No pulmonary or cardio-vascular complications occurred in which Fluothane could be implicated directly.

Five patients died in the postoperative period. One patient undergoing a lobectomy for tuberculosis developed a bleeding diathesis on the operating table which continued postoperatively despite vigorous therapeutic measures. She responded completely following anaesthesia, but developed pulmonary oedema and died 8 hours ofter operation. One patient died from severe pulmonary interstitial fibrosis 48 hours following a biopsy of the lung under anaesthesia. The other patients died from a cardiovascular accident four days after operation, pneumonia on the eighth day and from a brain tumour on the tenth day.

No deaths occurred during anaesthesia, but cardiac arrest developed in one patient. A 30-year-old white male, considered a good risk, came to the operating room for a right ureteral exploration following persistent right lower quadrant pain. Following a sleeping dose of pentothal sodium, 120 mg., he was induced and maintained with nitrous oxide, oxygen and Fluothane as described above. Endotracheal intubation was facilitated with succinylcholine, 50 mg., and respirations were controlled throughout the operation. After one and a half hours of uneventful anaesthesia, and as peritoneal closure was beginning, there was a sudden absence of pulse and blood pressure. No aortic pulsations were discernible, so an immediate left thoracotomy was performed and the heart found to be in asystole. Spontaneous cardiac rhythm returned one or two minutes after massage had started and the blood pressure rose rapidly to the previous level of 120/80. The patient made an uneventful recovery and suffered no apparent sequelae. It is impossible for us to assess the role of Fluothane in this cardiac arrest. It might very well be incriminated but, unfortunately, similar experiences have occurred in the past in which other anaesthetic drugs have been utilized.

Discussion

Whenever a new anaesthetic drug becomes available for clinical trial, the first reports are optimistic, later reports are more guarded in outlook, and finally, after several years, a more accurate assessment evolves. According to time relationships and also the brief experience of the authors, this report is optimistic in nature.

The anaesthesiologist needs a potent, non-inflammable and non-explosive inhalation drug. Fluothane possesses these virtues. In addition, induction of anaesthesia is rapid, salivary secretions are absent, pharyngeal and laryngeal reflexes are obtunded early, moderate degrees of muscular relaxation are provided in "surgical" planes, depth of narcosis can be varied rapidly and easily, and recovery occurs quickly with minimal nausea and vomiting.

The principal remaining mandatory attribute pertains to the *safety* of this compound in clinical practice. Does the administration of Fluothane endanger the life of the patient to a greater degree than drugs presently utilized to produce narcosis? The answer to this question may not be available for several years. However, opinions may be expressed, and ours is that this drug can be employed safely, *if administered properly and accurately.*

Proper clinical administration is related directly to the potency of Fluothane. Concentrations of Fluothane required for induction are 2 to 4 volumes per

cent and those needed for maintenance are 0.5 to 1.5 volumes per cent. The vaporizers at present available on anaesthetic gas machines in the United States, with the possible exception of the Foregger "copper kettle," do not allow one to deliver to the patient these low concentrations in a sufficiently precise manner for safe administration. Modification of present vaporizers, or new vaporizers, which permit variations of concentrations in tenths of volumes per cent are necessary for safe administration of Fluothane.

The potential hazards associated with Fluothane anaesthesia pertain to the respiratory, metabolic and cardiovascular systems. In "surgical" planes of anaesthesia the respiratory centre is depressed so that minute volume is decreased. This property of Fluothane should not be of concern to anaesthesiologists. Most of the drugs employed in daily practice depress respirations either centrally or peripherally. The manual assistance of respiratory exchange to maintain adequate alveolar ventilation should be second nature and as automatic as monitoring the pulse rate and blood pressure.

Interference with liver metabolism and a direct toxic effect on hepatic cells is a potential hazard of Fluothane which has not yet been ruled out. However, laboratory and clinical experiences to date have failed to demonstrate deleterious effects which would prohibit the use of the drug.

The action of Fluothane on the cardiovascular system is an important factor when related to safe usage. Hypotension from any cause is undesirable during operation, except under particular circumstances when it is induced intentionally. The falls in blood pressure seen with Fluothane can increase the hazard to the patient. However, it is our belief that accurate methods of vaporizing this drug will avoid much of the hypotension which is seen. In the present series the incidence of hypotension decreased as personnel became more familiar with the potency of the drug.

Cardiac arrhythmias in this series have not been more serious in nature and have been less frequent in incidence than those seen with cyclopropane. They can be checked quickly by lightening the plane of anaesthesia. At the present time it is believed that epinephrine should not be injected when Fluothane is being employed.

The contraindications or limitations to the use of Fluothane have been falling by the wayside with regularity. Because of its potency, it has not been utilized in infants under six months of age. The potential hypotensive action has prevented its use in patients suffering from shock or in those with minimal cardiac reserve, such as patients coming to operation for mitral commissurotomy. It has been avoided in patients with grossly disturbed cardiac rhythm such as auricular fibrillation. Otherwise it is believed that Fluothane can be administered with relative safety. That safety is enhanced by an accurate method of vaporization and a careful, watchful anaesthesiologist at the head of the table.

Acknowledgments

We wish to express our appreciation and thanks to our residents for their eager interest and to Mrs. Helen Parks for laboratory work.

Résumé

Le Fluothane, $CF_3CHClBr$, est un agent anesthésique par inhalation; il est puissant, non explosif et non inflammable; à l'Université Duke, nous l'avons administré à 500 malades pour en étudier les effets. Toutes sortes d'opérations ont été pratiquées chez des malades dont l'âge variait de 8 mois à 73 ans. Nous avons prescrit une prémédication ordinaire en surveillant toutefois que des doses adéquates de médicaments anticholinergiques soient administrées pour prévenir la bradycardie durant l'anesthésie.

Chez 27 enfants, nous avons fait l'induction en employant la technique du goutte à goutte. Chez le plus grand nombre des malades, nous avons fait l'induction en administrant une dose anesthésique de thiobarbiturate, puis nous avons continué en employant, en circuit semi-fermé, du protoxyde d'azote 2 litres, de l'oxygène 2 litres pour vaporiser le Fluothane. Nous avons employé différents vaporisateurs dont la plupart avaient été jaugés antérieurement. Pour l'induction, il a fallu employer des concentrations de 2 à 4 volumes pour cent. Pour le maintien de l'anesthésie, nous avons employé la même technique, mais des concentrations de 0.5 à 1.5 volumes pour cent. De cette façon, nous avons obtenu un certain degré de paralysie musculaire, mais, au cours des opérations sur la partie haute de l'abdomen, nous avons dû employer un paralysant musculaire, la succinylcholine; nous l'avons employée également dans la chirurgie thoracique pendant les explorations hilaires pour prévenir les réactions sur le tube endotrachéal.

Le Fluothane permet une induction rapide de l'anesthésie, sans sécrétions salivaires; il calme précocement les réflexes pharyngés et laryngés et, aux plans d'anesthésie chirurgicale, il procure un certain degré de relâchement musculaire; il permet un contrôle facile de la profondeur de l'anesthésie; le réveil est rapide et s'accompagne d'un minimum de nausées et de vomissements.

Quand l'anesthésie est aux plans chirurgicaux, le centre respiratoire est déprimé au point que, chez presque tous les malades, il faut assister la respiration. Cette propriété ne doit pas être un inconvénient pour l'anesthésiologiste.

Plus particulièrement au cours de l'induction, nous avons observé de l'hypotension qui a dépassé 20 mm. Hg chez 41 pour cent des malades. Chez tous les malades, à l'exception de 16, la pression sanguine est revenue à la normale sans que nous ayons dû recourir à une thérapeutique spéciale. L'incidence de l'hypotension a diminué à mesure que le personnel est devenu plus familier avec le pouvoir du médicament.

En employant les composés halogénés, il faut porter une attention spéciale aux manifestations hépatatoxiques. Au cours de cette épreuve, les tests de glycémie et le bromesulphaléine n'ont pas donné de résultats différents des cas témoins.

La sécurité de l'administration du Fluothane tient à la reconnaissance de sa puissance anesthésique. Dans le moment, l'appareil à notre disposition aux Etats-Unis ne nous donne pas assez de précision pour l'administration des faibles concentrations nécessaires. Il faudrait avoir des vaporisateurs nouveaux ou

modifier ceux que nous avons dans le moment. Nous avons la conviction que le Fluothane va avoir sa place comme anesthésique.

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FLUOTHANE FOR PAEDIATRIC ANAESTHESIA*

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A CLINICAL EVALUATION of Fluothane as applied to paediatric anaesthesia was carried out. No special metabolic studies were done. Fluothane was administered to 300 patients, ranging in age from 5 hours to 18 years (Table I), and in weight from 5½ to 184 pounds. This agent was used in the anaesthetic management of almost every type of surgery (Table II). Patients undergoing cardiovascular surgery were omitted from this study.

TABLE I

DISTRIBUTION OF CASES ACCORDING TO AGE

Age	Number
During 1st week of life	3
1 week to 6 months	31
6 months to 2 years	57
2 years to 5 years	74
5 years to 10 years	86
Over 10 years	49
Total	300

TABLE II

TYPES OF SURGERY

Type	Number
Head and neck (excluding intracranial)	91
Intracranial	5
Thoracic	3
Abdominal	62
Plastic (excluding head and neck)	50
Orthopaedic	25
Adenotonsillectomy (induction only)	25
Endoscopy	17
Cystoscopy	9
Neurological investigation	13
Total	300

PREMEDICATION (Table III)

Bradycardia has been reported during the administration of Fluothane. Premedication with atropine sulphate has been recommended for its prevention (1). With a routine dose of atropine sulphate (½) an average of the slowest cardiac rates observed by us during operation was 122 beats/min. The average of the slowest rates in the unpremedicated cases was 105 beats/min. Atropine also rendered the cardiac rate less labile. Changes in rate subsequent to changes in

*Fluothane used in this study was supplied by Ayerst, McKenna and Harrison Ltd., through the courtesy of Dr. Leighton Smith.

†From the Department of Anaesthesia, Hospital for Sick Children, Toronto, Canada.

TABLE III

PREMEDICATIONS USED

Premedication	Number
Unpremedicated	78
Atropine sulphate	123
Demerol and atropine sulphate	97
Other combinations	2
Total	300

vapour concentration were of a smaller magnitude than those observed when premedication was omitted.

The inclusion of Demerol in the premedication did not appreciably alter the concentration of Fluothane required for maintenance, and resulted only in a slight prolongation of recovery time.

METHODS OF ADMINISTRATION

The open drop technique provided rapid induction and an easily controlled maintenance phase.

Insufflation of the airway with Fluothane vapour, nitrous oxide, and oxygen was the technique used in bronchoscopy and for most infants and younger children. Four methods of insufflation were employed: (*a*) under an open mask, (*b*) with an oropharyngeal airway, (*c*) through the side arm of a bronchoscope, and (*d*) by means of a modified Ayer's tube.

A non-rebreathing technique employing the Stephen–Slater valve was used in most of the older children.

The closed technique with carbon dioxide absorption was not employed in this series.

EQUIPMENT

Fluothane was vaporized by passing mixtures of nitrous oxide and oxygen over its surface in several standard types of ether and trichlorethylene vaporizer. Although these methods proved adequate, the extreme potency of the agent necessitated a considerable amount of practice to establish the range of settings that would give reproducible clinical effects. Once stabilized, the depth of anaesthesia could be markedly altered by minute changes in the vaporizer setting.

A "Fluotec"[1] vaporizer was employed in 128 cases. Designed especially for the administration of Fluothane, this vaporizer delivers a fixed concentration of vapour over a broad range of temperatures and gas flows for periods up to one hour. The 0.1 per cent intervals with which the apparatus is calibrated rendered the administration of Fluothane dependable and easy. All percentage concentrations mentioned in the body of this paper will refer to settings on the Fluotec Vaporizer.

[1]Manufactured by Cyprane Ltd., Keighley, England. Loaned for this study by Canam Surgical Services Ltd., Toronto, through courtesy of Mr. Fraser Sweatman.

Induction

Anaesthesia was induced on 44 occasions with the open drop technique. Fluothane was comparable to chloroform in the amount required and the rapidity of induction. Patients passed rapidly through the first and second stages with less excitement than seen with other commonly used volatile agents. Although several children objected to the odour of the vapour, irritation was minimal, and coughing occurred in only one case. Salivation was depressed, even in unpremedicated patients. The transition to open ether, when used, was very smooth with quiet respiration free from laryngospasm, coughing, retching, or salivation.

Anaesthesia was induced on 71 occasions with 60–80 per cent nitrous oxide, oxygen, and Fluothane, administered by either the insufflation or non-rebreathing technique. The effects were the same as those seen with open drop induction. A gradual increase in the concentration of Fluothane vapour was most easily obtained with the Fluotec vaporizer. Patients on whom this apparatus was used exhibited the smoothest induction that the writers have encountered. A 2 per cent concentration was required for almost all patients and exceeded 2.5 per cent on only one occasion.

Maintenance

(1) *With inhalation agents only.* During the initial investigation of Fluothane we made a habit of adding a little ether vapour to the mixture of gases for about three or four minutes before intubation or incision. This was done in order to avoid any reflex movement of the patient and the inevitable "surgical" condemnation of a new drug. Broader experience and greater confidence has enabled us to omit this addition for certain patients.

Fifty-one procedures were performed under Fluothane alone or in combination with nitrous oxide and oxygen. Only moderate relaxation was required for this group: incision of abscesses, reduction of simple fractures, soft-tissue orthopaedics, plastic procedures, mastoidectomies, and bronchoscopic *suctions.* The latter required insufflation of up to 3 per cent Fluothane through the bronchoscope. The other procedures required only 0.7–1.0 per cent for maintenance.

We have continued to add ether for opening and closing peritoneum and for bronchoscopies other than simple suctions in order to avoid over-dosage with Fluothane.

(2) *With relaxants and/or barbiturates for induction.* Fluothane was the principal agent following induction with a variety of barbiturates: thiopental in 91 cases, methitural in 42 cases, and buthalitone in 18 cases. Relaxation appropriate to the procedures was achieved with succinylcholine, decamethonium, or d-tubo curare. Although a few patients required up to 1.5 per cent Fluothane to establish anaesthesia, the majority were readily established with 1.0 per cent. Subsequent reductions in concentration were made in all cases. Almost all patients were easily maintained with 0.7–0.8 per cent settings.

Fluothane following d-Tubo Curare

Bryce-Smith and O'Brien have warned against the administration of curariform agents to patients under Fluothane anaesthesia (3). The reported effects have

been bradycardia and profound hypotension. Fluothane was administered to 48 patients in this series *following* the injection of d-tubo curare. Abdominal relaxation was achieved with doses of 1 mg./10 lbs. Patients requiring only moderate relaxation received 1 mg./15 lbs. A bradycardia of 72 beats/min. was observed in only one patient. The systolic pressure of one patient fell from 110 to 60 mm. Hg when 2.5 per cent Fluothane was administered following the larger dosage of d-tubo curare. Reducing the Fluothane concentration to 1.5 per cent resulted in a prompt return of pressure to normal levels.

Use of Adrenalin with Fluothane

Varying volumes of procaine 1.0 per cent with added adrenalin (1:60,000) were injected subcutaneously in 21 patients undergoing plastic surgery. The only effects noted were a slight increase in cardiac rate (10–20 beats/min.) accompanied by a slight increase in respiratory rate. No arrhythmias were observed clinically. Continuous monitoring with the electrocardiograph was not done.

Recovery from Anaesthesia

Recovery from anaesthesia was characterized by a complete return of the sensorium at an extremely rapid rate. The average time for complete recovery with various anaesthetic combinations was observed by one of us (C.S.) (Table IV). A tendency to fall asleep following recovery was rarely observed.

Although no records were kept of the number of postoperative emeses, the absence of vomiting was a noticeable feature of the recovery period.

TABLE IV

Average Recovery Times following Fluothane

Anaesthetic combinations	Average time (min.)	Number of cases
Fluothane (alone and with N_2O:O_2)	7.2	35
Fluothane with added ether	10.4	55
Thiopental induction+Fluothane	11.4	14
Methitural induction+Fluothane	7.7	38
Buthalitone induction+Fluothane	8.7	18

Assessment

Fluothane can be administered by simple techniques. Because of its potency a method of obtaining precise concentrations is preferred.

As salivary secretions are diminished, premedication with drying agents may be omitted. Atropine is advisable, however, for the prevention of bradycardia resulting from higher Fluothane concentrations.

The absence of irritation rendered Fluothane highly acceptable to the great majority of children. This acceptance together with its rapid action and freedom from side effects makes Fluothane a very useful induction agent. Induction by the open drop technique should be *drop by drop* to avoid overdosage which can easily occur.

Relaxation of the jaw occurs early. Intubation or endoscopy can be readily performed providing anaesthesia has been maintained for about five minutes. With shorter induction periods recovery is so rapid that difficulties may be experienced both during and immediately following intubation.

Levels of anaesthesia deeper than stage III, plane 2, were attended by respiratory depression and bradycardia. Supplementation with either relaxants or ether is recommended for abdominal relaxation.

Insufflation of Fluothane is effective for bronchoscopic suctions in which some degree of coughing is desirable. Other endoscopic procedures, such as removal of foreign body and bronchography, require the addition of ether for a quiet operating field.

Formerly, intravenous cut-downs were employed in some infants for the sole purpose of administering non-explosive agents. The non-inflammable quality of Fluothane offers a useful alternative wherever explosion hazards are encountered.

The rapid uncomplicated recovery following out-patient procedures is advantageous.

Changes in the size of the pupils provide a guide to anaesthetic depth. The myosis of the upper third stage is more intense than that seen with any other agent.

As a drug, Fluothane is an excellent hypnotic, a good analgesic, and a moderate relaxant.

Summary

Fluothane was administered to 300 patients ranging in age from 5 hours to 18 years, and in weight from 5.5 to 184 pounds. It was used in all types of operations, either alone or in combination with all other agents in routine use.

All inhalation techniques other than closed were used. The preferred method of administration was by means of a "Fluotec" vaporizer, but other standard types of vaporizers and open drop methods were satisfactory.

Unconsciousness could be produced rapidly and smoothly, without laryngospasm or vomiting.

Good first and reasonably satisfactory second plane surgical anaesthesia could be produced. For deeper planes of anaesthesia supplementation by other agents was preferred to the use of greater concentrations of Fluothane.

A rapid return of a clear sensorium, even after prolonged anaesthesia, was a dominant feature of the recovery period. Nausea and vomiting were minimal.

The side effects noted were: marked myosis, decrease in salivation, decrease in cardiac rate with increasing depth of anaesthesia, absence of sweating, and frequent tearing. Hypotensive effects were infrequent and not severe.

Fluothane is an excellent hypnotic, a good analgesic, but only a moderate relaxant. The extreme potency of the agent recommends it for use by the qualified anaesthetist only.

Résumé

Nous avons administré le Fluothane à des malades dont l'âge variait de 5 heures à 18 ans et dont le poids allait de 5½ livres à 180 livres. Nous l'avons employé

pour toutes sortes d'opérations. Nous l'avons employé seul ou associé à tous les agents d'usage courant.

Nous avons employé toutes les techniques pour inhalation sauf le circuit fermé. La méthode que nous préférons est celle du vaporisateur "Fluotec" quoique les autres sortes de vaporisateurs et le goutte à goutte nous ont donné de bons résultats.

Nous avons pu produire l'inconscience de façon rapide et douce, sans spasmes laryngés et sans vomissements.

Nous avons atteint comme niveau d'anesthésie un premier plan et même un deuxième plan chirurgical. Quand un plan plus profond était nécessaire, nous avons préféré associer d'autres agents plutôt que d'augmenter les concentrations du Fluothane.

La période du réveil a été caractérisée par un retour rapide à la lucidité même après des anesthésies de longue durée. Les nausées et les vomissements sont réduits au minimum.

Les effets secondaires observés sont: un myosis marqué, une diminution de la salivation, un ralentissement du rythme cardiaque à mesure que s'approfondit l'anesthésie, une absence de transpiration et du larmoiement fréquent. Nous n'avons observé de l'hypotension qu'occasionnellement et elle n'a pas été prononcée.

Le Fluothane est un hypnotique de première qualité, un bon analgésique mais il ne donne qu'un faible relâchement musculaire. Le fort pouvoir anesthésique de cet agent nous incite à recommander que des anesthésistes qualifiés seulement en fassent usage.

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THE USE OF FLUOTHANE IN ANAESTHESIA FOR NEUROSURGERY: A PRELIMINARY REPORT

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Pharmacological studies (1) and early clinical reports (2, 3, 4) have attributed to trifluorobromchlorethane ($CF_3CHClBr$, Fluothane) a combination of pharmacological actions unique among the volatile anaesthetic agents. Ready controllability, rapid postoperative elimination, adequate potency, a reversible hypotensive action and absence of explosive properties are obvious advantages in the anaesthetic management of the neurosurgical patient.

This report is concerned with 107 administrations of Fluothane for minor and major neurosurgical procedures. The results of liver function tests performed on 31 patients will be presented, certain clinical observations and the impressions derived therefrom will be assessed and discussed, and an evaluation will be attempted of electrocardiographic records obtained on 31 occasions in 29 patients.

Clinical Material

The distribution of the patients by age and sex and a broad classification of the operations performed, including the range and average duration, are shown in Tables I and II.

TABLE I

	Age									
	0–2	3–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	Total
Male	6	6	2	9	16	7	5	2	1	54
Female	2	3	4	4	6	8	5	2	–	34
Total	8	9	6	13	22	15	10	4	1	88

TABLE II

Operation	No.	Average duration and range (min.)
Superficial, cranial and extracranial	20	162 (80–360)
Intracranial	35	264 (60–500)
Spinal	23	260 (60–570)
Radiological investigations	30	101 (60–240)
Total	108	199

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METHOD

In most instances premedication was atropine alone; variations in premedication are shown below.

Premedication	*No. of patients*
Atropine only	79
Atropine and Demerol	6
Atropine and barbiturate	3
Atropine and codeine	5
Atropine and Benadryl	1
Atropine and Phenergan	1
Largactil, Phenergan, Demerol	8
Nil	5
Total	108

On 85 occasions, which included all adults, anaesthesia was induced with thiopental in amounts not exceeding 500 mg., followed by succinylcholine chloride up to 50 mg.; laryngeal intubation was preceded by topical application of 10 per cent cocaine or 4 per cent lidocaine. Anaesthesia was induced with nitrous oxide–oxygen–Fluothane on 21 occasions in children and infants; for 2 infants cyclopropane was used.

For 78 procedures a non-rebreathing technique was employed to administer nitrous oxide–oxygen–Fluothane, using the Stephen-Slater valve or the Fink modification. The oxygen percentage in the mixture was maintained above 30. The Marrett head of the Air-Med apparatus, modified for administration of high flows of nitrous oxide oxygen, was convenient and proved very satisfactory in practice. Fluothane was administered from the "Trilene" vaporizer filled to the 2 fluid ounce level and maintained as close to that level as possible thereafter. The concentrations of Fluothane delivered (volumes per cent), using a total flow rate of 10 litres per minute, are: 0.5 per cent at the first mark on the vaporizer, 1.0 per cent at the second, and 1.5 per cent at the third (5). A 1 per cent concentration of Fluothane was almost invariably employed for maintenance of anaesthesia. Concentrations above 2 per cent (reached midway between mark 3 and "on") were rarely used.

For thirty radiological investigations under anaesthesia an unmodified Marrett head was utilized; high flow rates of gases were administered in a semi-closed system with a fully open expiratory valve.

Electrocardiographic tracings were obtained with a Sanborn Viso-Cardiette during thirty-one major neurosurgical procedures. With two exceptions local anaesthetic (Nupercaine, 1/1500) with added adrenaline (1/250,000 of free base) was injected, by the surgeon, in amounts close to 125 ml. Blood samples were withdrawn from three patients about ten minutes after the injection of local anaesthetic with added adrenaline. Plasma adrenaline and noradrenaline were estimated by a modification (6) of the method of Von Euler and Floding (7).

Four tests of liver function were performed on thirty-one patients. About one hour prior to operation blood was withdrawn for determination of serum bilirubin and prothrombin time, and for the cephalin-cholesterol flocculation test; brom-

sulphalein was injected (5 mg./kg.) and 45 minutes later blood was withdrawn in order to determine bromsulphalein excretion. The tests were repeated on the first, the third or fourth and finally the seventh day after the operation.

Results

Liver Function Tests

Retention of bromsulphalein occurred preoperatively in four seriously ill patients, in whom the postoperative findings are shown in Table III. Further increases

TABLE III

INCREASED PREOPERATIVE BROMSULPHALEIN RETENTION

Patient	Operation	Duration (hrs.) (min.)	Preop. (%)	Number of days after operation 1	3 (%)	7
1	Incision and repacking	3 0	50	40	—	40
2	Hypophysectomy	7 30	50	30	22.5	22
3	Craniotomy	3 20	10	24	20	22
4	Hypophysectomy	6 30	13	25	—	8
	AVERAGE	5 5	30.8	29.8	21.3	23

TABLE IV

NORMAL POSTOPERATIVE BROMSULPHALEIN RETENTION

Patient	Operation	Duration (hrs.) (min.)	Preop. (%)	Number of days after operation 1	3 (%)	7
1	Cervical laminectomy	3 40	2	2	2	3
2	Lumbar discoidectomy	3 10	3.5	5	5	3.8
3	Carotid angiogram	1 40	2	3	5	2
4	Lumbar discoidectomy	6 0	2	1.8	2	2
5	Spinal fusion	4 40	2	2	2	—
6	Cervical laminectomy	8 0	2	2	5	2
7	Repair of CSF leak	3 0	3	1.5	—	—
8	Cervical laminectomy	5 15	2	2	2	1
9	Craniotomy	6 10	2	2	2	5
10	Frontal débridement	2 0	2	2	2	1
11	Craniotomy	4 45	2	6	2	2
12	Lumbar discoidectomy	5 0	2	3	2	2
13	Lumbar discoidectomy	3 30	1	2	2	3
14	Re-opening craniotomy	8 30	4	6	5	2
15	Lumbar discoidectomy	4 15	1	1	1	1
16	Spinal fusion	4 10	1	1	2	2
17	Craniotomy	4 45	6	8	6	5
18	Lumbar discoidectomy	6 0	2	8	2	2
19	Lumbar discoidectomy	4 0	2	3	3	1
	AVERAGE	4 39	2.3	3.2	2.9	2.3

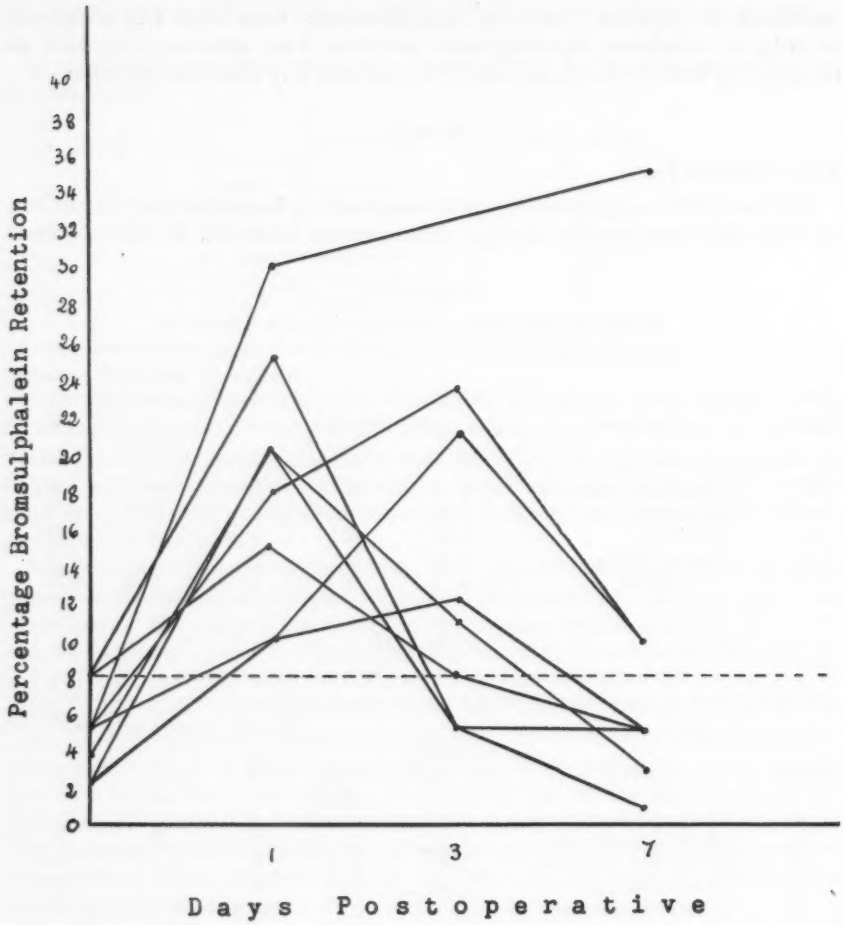

FIGURE 1. Increased postoperative bromsulphalein retention.

occurred in two of these patients. Pre- and postoperative values below 8 per cent, considered to be within normal limits, were obtained in nineteen patients, as shown in Table IV. Estimations of total serum bilirubin were within normal limits (below 1 mg. per cent) in all cases with a single possible exception: one patient showed a preoperative value of 0.8 mg. per cent rising to 1.3 and 1.0 mg. per cent on the first and third postoperative days, returning to 0.5 mg. per cent by the seventh day. In this patient bromsulphalein retention, which increased from 2 per cent preoperatively to 20 per cent and 11 per cent on the first and third postoperative days respectively, returned to a normal 3 per cent on the seventh day. The cephalin-cholesterol flocculation test was within normal limits ("one plus" or "negative") in all patients at all times. According to the data

TABLE V

INCREASED POSTOPERATIVE BROMSULPHALEIN RETENTION

Patient	Operation	Duration (hrs.)(min.)	Preop. (%)	Number of days after operation 1	3 (%)	7
1	Cervical discoidectomy	3 40	2	10	12	5
2	Lumbar discoidectomy	3 20	5	30	—	35
3	Craniotomy	7 0	8	15	8	5
4	Craniotomy	3 30	5	10	21	10
5	Craniotomy	6 0	8	25	5	5
6	Cervical laminectomy	9 30	3	20	5	1
7	Craniotomy	4 10	5	18	23.5	10
8	Craniotomy	5 05	2	20	11	3
	AVERAGE	5 27	4.7	18.5	12.2	9.2

obtained, no significant increases in prothrombin time occurred. Increased retention of bromsulphalein after Fluothane anaesthesia was found in eight patients who showed normal preoperative values (Table V; Fig. 1). If the two patients who showed increased bromsulphalein retention preoperatively are included, the incidence of abnormal postoperative findings which can be directly related to Fluothane anaesthesia in this series of thirty-one patients becomes 32 per cent; of these ten patients, six showed a maximal rise on the first postoperative day; in four patients the rise was maximal on the third postoperative day. By the seventh day normal values were restored in six and nearly normal values in two patients. In two cases the values on the seventh postoperative day were abnormal, although in one of these the preoperative value had also been increased.

CLINICAL OBSERVATIONS

A generally favourable impression of Fluothane has been gained as a result of 108 administrations to 88 neurosurgical patients.

In 21 inductions with nitrous oxide–oxygen, transition to Fluothane-oxygen was smooth, without irritation or mucous secretion in the respiratory tract. After induction with thiopental and succinylcholine, Fluothane anaesthesia can be established quickly and uneventfully.

Eventful administrations	*No.*
Difficulty in inducing anaesthesia	1
Anaesthesia adequate, vasopressors required	8
Circulatory depression, anaesthesia inadequate, vasopressors required	3
Steady state of anaesthesia disturbed by surgical stimuli	7
Hypotension and respiratory depression	2*
Airway obstruction	1
Auricular fibrillation	1*
Total	21

*Two patients requiring vasopressor therapy are also included under the headings "respiratory depression" and "auricular fibrillation."

Those Fluothane administrations which require further comment are listed on the preceding page.

Difficulty was encountered with a 4-month-old baby: after a cyclopropane induction, endotracheal Fluothane-oxygen was started, but a steady state of anaesthesia could not be achieved. The baby was satisfactorily anaesthetized with ether.

In five adults and one child, when anaesthesia had been carefully assessed and considered satisfactory, surgical stimulation subsequently induced coughing, straining or reflex movement. A 3-year-old child showed prolonged extensor spasms of the limbs although concentrations of Fluothane above 2 per cent were administered.

In this series hypotension has occurred frequently during Fluothane anaesthesia. Table VI lists the lowest and the highest systolic blood pressures observed. In 45 per cent of 101 administrations the lowest systolic blood pressure was at some time in the range 80–100 mm. Hg. Changes in heart rate have been less noteworthy (Table VII).

Table VIII gives the lowest and highest respiratory rates recorded during 68 administrations; tachypnoea was relatively frequent.

TABLE VI

SYSTOLIC BLOOD PRESSURES
(101 patients)

Systolic B.P.	< 60	61–80	81–100	101–120	121–140	> 140
Lowest	8	16	46	26	5	—
Highest	—	—	27	45	22	7

TABLE VII

HEART RATES
(101 patients)

Heart rate	< 60	61–80	81–100	101–120	120
Slowest	7	42	41	14	4
Fastest	—	20	45	28	15

TABLE VIII

RESPIRATORY RATES
(68 patients)

Respiratory rate	< 10	11–20	21–30	31–40	41–50	51–60
Slowest	1	21	36	10	0	0
Fastest	0	4	36	24	2	2

With Fluothane an adequate plane of surgical anaesthesia may not be maintained without concomitant hypotension. One example may be noted.

A 59-year-old female patient was anaesthetized and postured in the semi-recumbent position for sub-temporal exploration of the fifth cranial nerve. No local anaesthetic was employed. During the surgical approach anaesthesia appeared adequate, but systolic pressure was 75–85

mm. Hg. Stimulation of the fifth nerve produced immediate coughing and straining; to restore a steady state of anaesthesia 250 mg. of thiopental was given over the next five minutes. The hypotension induced by Fluothane was not potentiated by thiopental in this patient, the blood pressure being maintained at 80–90 mm. Hg.

In three patients vasopressor therapy was necessary to maintain with safety an adequate depth of anaesthesia. During a craniotomy the concentration of Fluothane was decreased because of sudden hypotension (to 80 mm. Hg); the patient responded by moving, and satisfactory conditions could only be restored by increasing the concentration of Fluothane and employing a continuous neosynephrine infusion. Another patient developed hypotension (to 60 mm. Hg) when anaesthesia was deepened after a bout of coughing during lumbar discoidectomy; intravenous vasoxyl, 5 mg., followed by a neosynephrine infusion, permitted satisfactory operating conditions for the remaining hour of operation. Again, a hypertensive patient undergoing lumbar discoidectomy required 20 mg. of vasoxyl and a continuous neosynephrine infusion over a three-hour period.

Vasopressor therapy was necessary in seven patients because of hypotensive states occurring in the course of satisfactory anaesthesia. In two of these patients blood loss may have been a contributing factor. Intravenous vasoxyl, 2–5 mg., has been found entirely satisfactory to counteract hypotension during Fluothane anaesthesia. Neosynephrine infusions (20 mg./500 ml.) are equally effective and may be more convenient during prolonged operations.

In two patients with spinal cord lesions, extreme sensitivity to the hypotensive action of Fluothane was apparent. No such effect has been observed with ether anaesthesia.

A 25-year-old male patient with a spinal cord tumour at D4 level developed respiratory depression when the systolic pressure fell abruptly to 65 mm. Hg within a few minutes of starting endotracheal Fluothane-oxygen anaesthesia. A prompt response to 5 mg. of intravenous vasoxyl was obtained; ether was substituted for Fluothane and a blood pressure of 100 mm. could be maintained while ether was given. On two subsequent occasions administration of Fluothane was resumed (concentration about 1 per cent), and blood pressure again became depressed to levels of 70 and 80 mm. Hg. Similarly in a 22-year-old man with a spinal cord transection at C5 level, blood pressure fell from 110 to 75 mm. after some minutes of Fluothane anaesthesia; severe respiratory depression was also present. Substitution with ether brought rapid improvement, with increased respiratory amplitude and a rise in blood pressure to 110 mm. Hg. Resumption of Fluothane anaesthesia after one hour again produced circulatory and respiratory depression.

A very obese 65-year-old female patient, admitted to hospital following a fall (probably preceded by a fainting attack), developed auricular fibrillation following induction with Fluothane anaesthesia. This patient was hypertensive (B.P. 210/110) and showed considerable drowsiness after air ventriculography. A subdural haematoma was diagnosed and evacuated without incident. Anaesthesia for this operation was induced by thiopental 500 mg., Anectine® 50 mg., followed by nitrous oxide oxygen ether; ether was replaced by Fluothane on transfer to the operating room. Hypotension was easily induced by Fluothane, but was readily reversed by discontinuing the volatile supplement for short periods. Tachycardia up to 130 per minute was observed during and after this operation.

Seizures subsequently developed and the patient was unconscious when brought to the operating room for a second craniotomy two days after the first operation. While thiopental (275 mg.) was being given the patient had a short seizure. After relaxant and intubation systolic blood pressure was 130 mm. (preoperatively 180 mm.). Administration of Fluothane and oxygen by closed circuit (Heidbrink) for approximately two minutes produced systolic

hypotension to below 60 mm. This was not immediately treated with vasopressors, the view being taken that a satisfactory level of blood pressure would be regained on discontinuing Fluothane. This expectation was not realized, and a delay of five to ten minutes occurred before a blood pressure above 100 mm. systolic was achieved by infusion of neosynephrine (20 mg./500 ml.). Heart rate was now very fast and irregular. The operation was started, electrocardiographic tracings showing rapid auricular fibrillation (Fig. 2A).

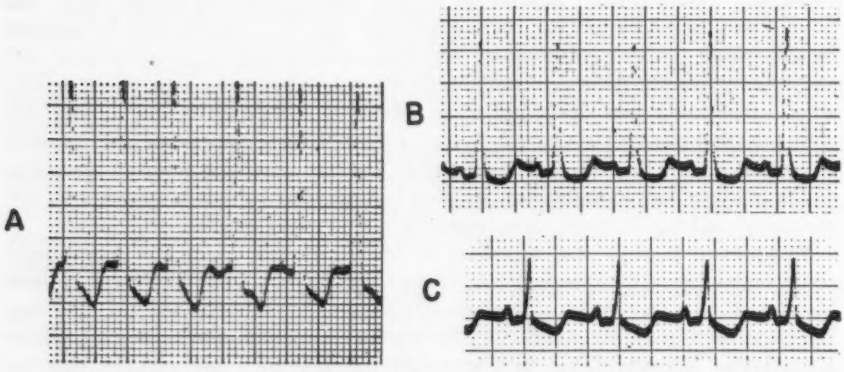

FIGURE 2: A, during operation—auricular fibrillation; B, after operation—supraventricular tachycardia; C, first postoperative day—changes in *T* wave and *ST* segment.

Blood pressure was maintained throughout operation at 100–140. mm.; neosynephrine was no longer required after a total dose of 10 mg. injected over 30 minutes. Oübaine (0.45 mg.) was given in divided doses in an unsuccessful attempt to reduce heart rate which persisted throughout at 160 per minute.

At the end of operation, after anaesthesia lasting three hours, systolic blood pressure was 120 mm., heart rate 160. An electrocardiogram 50 minutes after operation showed a sinus rhythm of 140 per minute (Fig. 2B). The patient remained unconscious although reacting; digitalisation maintained heart rate at about 110 per minute. On the first postoperative day changes in the *T* wave and *ST* segment were apparent (Fig. 2C); hypertension persisted at levels up to 220/120 mm. Blood pressure began falling on the fifth postoperative day and death occurred six days after the second operation.

Autopsy report demonstrated the following pathological changes in this patient: an extradural haematoma in the posterior fossa; a basal skull fracture related to the left transverse sinus; multiple left pulmonary infarcts of undetermined origin; hypertensive arteriosclerotic disease with hypertrophy of the left side of the heart.

A healthy male patient, 57 years of age, was induced normally with thiopental 400 mg. and succinylcholine 40 mg., followed by light endotracheal Fluothane anaesthesia during posturing in the face down position for exploration of a cervical cord tumour. The electrocardiographic pattern was normal (Fig. 3A). The few minutes required for transfer to the operating room permitted lightening of anaesthesia; as the surgeon was injecting local anaesthetic (with added adrenaline), administration of 1.5 per cent Fluothane in 50 per cent nitrous oxide–oxygen failed to establish a satisfactory plane of anaesthesia; dislodgement of the mouth gag and compression of the endotracheal tube by the patient's gums resulted in moderate airway obstruction. Electrocardiographic monitoring, resumed in the operating room, within two minutes of local injection revealed ventricular extrasystoles (Fig. 3B).

Ten minutes following injection of local (with added adrenaline) and after relief of the airway obstruction, the tracing demonstrated multifocal ventricular extrasystoles (Fig. 3C). Systolic blood pressure was in the range 120–140 mm. Hg. Surgery commenced and Fluothane

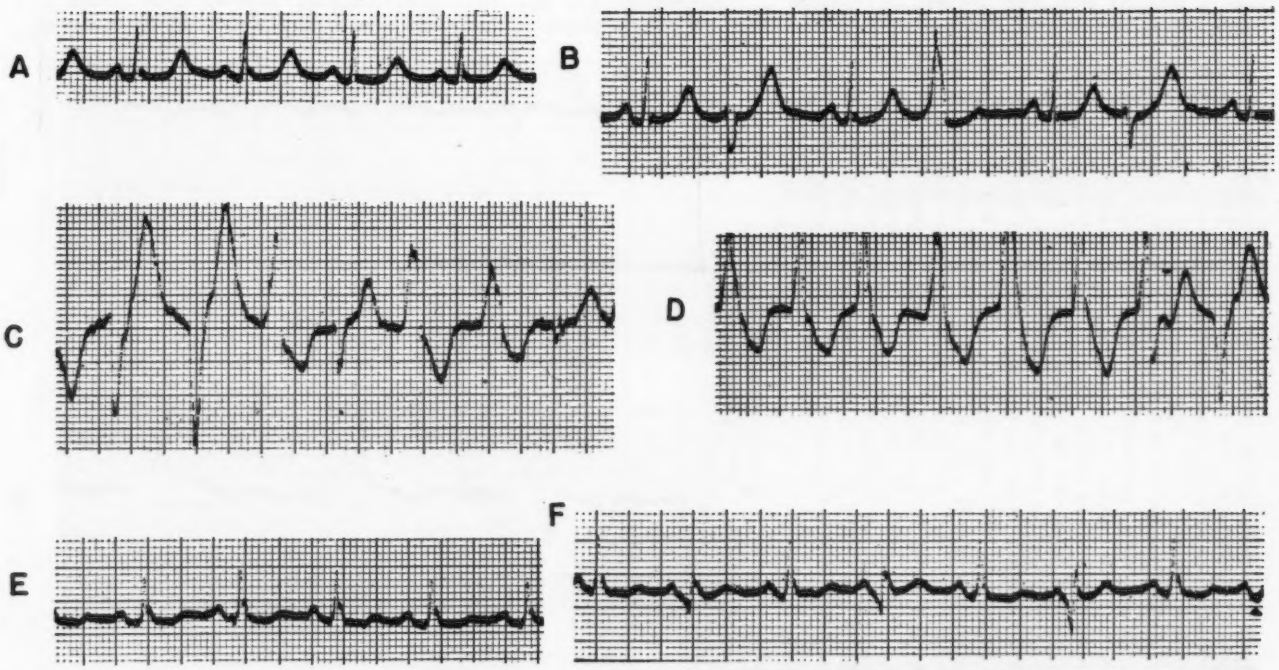

FIGURE 3: A, after induction—sinus rhythm; B, 1 minute, 45 seconds after adrenaline injected with local—bifocal ventricular extrasystoles; C, 10 minutes after local—multifocal ventricular extrasystoles; D, 55 minutes after local—multifocal ventricular tachycardia; E, 7 minutes after starting ether—sinus rhythm; F, 1½ minutes after resuming Fluothane—interpolated ventricular extrasystoles.

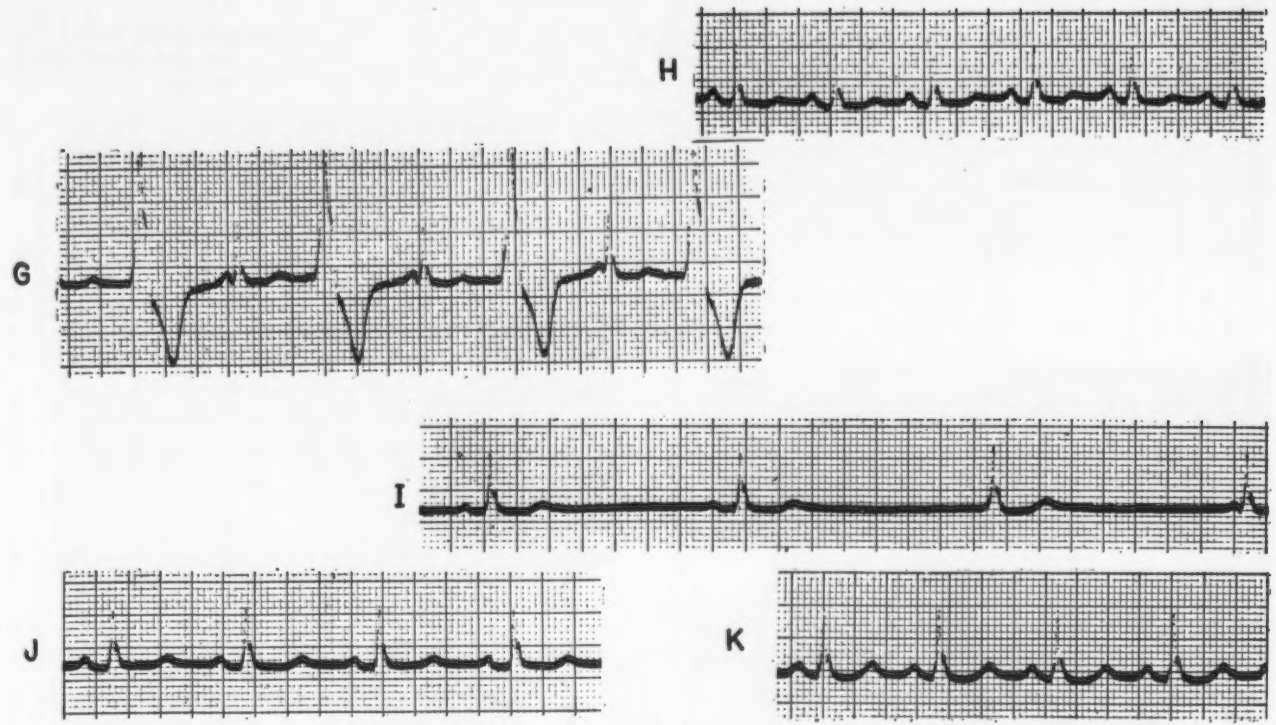

FIGURE 3: G, 15 seconds later—nodal rhythm, with bigeminal ventricular extrasystoles; H, 2 minutes after starting ether—sinus rhythm; I, 3 minutes after resuming Fluothane—bradycardia with A-V dissociation; J, 2 minutes after starting ether—sinus rhythm; K, after 100 minutes of Fluothane—sinus rhythm.

was continued for a further period of 40 minutes, during which time frequent bursts of ventricular extrasystoles were observed. Fluothane was discontinued 55 minutes after the injection of local, when the tracing still showed gross irregularities and tachycardia (Fig. 3D). Ether was given (via the Marrett vaporizer), and during the next few minutes cardiac rhythm gradually became normal. Sinus rhythm was established seven minutes after changing to ether anaesthesia (Fig. 3E). Ether was discontinued and Fluothane again administered in a concentration of approximately 1 per cent. One minute, thirty seconds later, interpolated extrasystoles appeared (Fig. 3F). Fifteen seconds later a bigeminal rhythm became established in which nodal rhythm was coupled with ventricular extrasystoles (Fig. 3G). Fluothane was stopped and ether anaesthesia resumed; two minutes later sinus rhythm (rate 96 per minute) reappeared (Fig. 3H). Fluothane was again administered, two hours and twenty-five minutes after local injection. Three minutes later there was pronounced bradycardia (rate 38 per minute) with A-V dissociation (Fig. 3I). Fluothane was discontinued and ether anaesthesia resumed. Two minutes later sinus rhythm (rate 72 per minute) was again established (Fig. 3J). Fluothane was restarted; blood pressure, which had been maintained throughout the period of arrhythmia at 110–150 mm. Hg, now showed a sudden fall to 85 mm. Hg which lasted less than five minutes. Fluothane was then continued for the last hundred minutes of operation without further arrhythmia or hypotension. Electrocardiographic tracings at the close of operation (Fig. 3K) show sinus rhythm (rate 82 per minute).

Electrocardiography

Electrocardiographic records were obtained during 31 administrations of Fluothane. In addition to the patient previously mentioned who had auricular fibrillation, changes were observed during 15 administrations on 14 patients. Patterns observed in twelve patients during Fluothane anaesthesia, and apparently

TABLE IX

Electrocardiographic Changes during Fluothane

	Fluothane (apparently unrelated to adrenaline)	Fluothane and adrenaline (within 30 minutes of injection of adrenaline)
I. Changes in rhythm		
Sinus tachycardia	1	1
Sinus bradycardia	1	–
Nodal rhythm	2	1
Auricular fibrillation	1	–
Shifting pacemaker	2	3
A–V dissociation	2	1
Extrasystoles		
Supraventricular	1	–
Ventricular		
Isolated	–	2
Interpolated	1	–
Bigeminal rhythm	–	2
Mnultifocal	–	1
Vetricular tachycardia	–	1
II. Depression of:		
P wave	–	2
ST segment	–	4
T wave	–	4

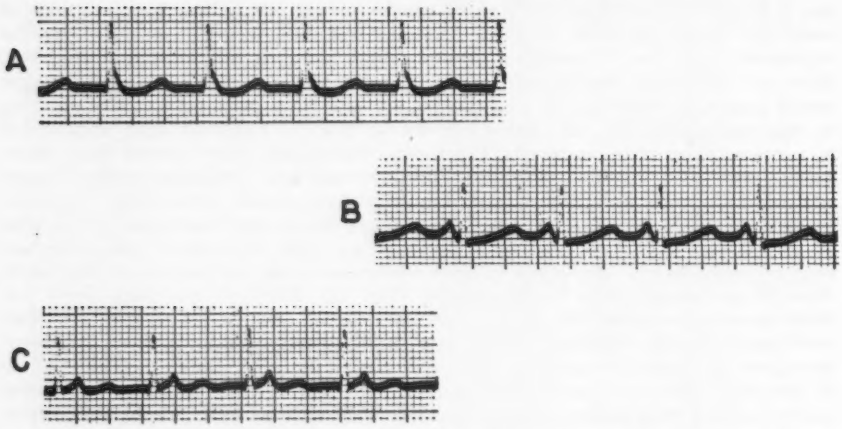

FIGURE 4: A, nodal rhythm; B, 15 seconds later–shifting pacemaker; C, 5 minutes later–shifting pacemaker–*P* wave between *QRS* complex and *T* wave.

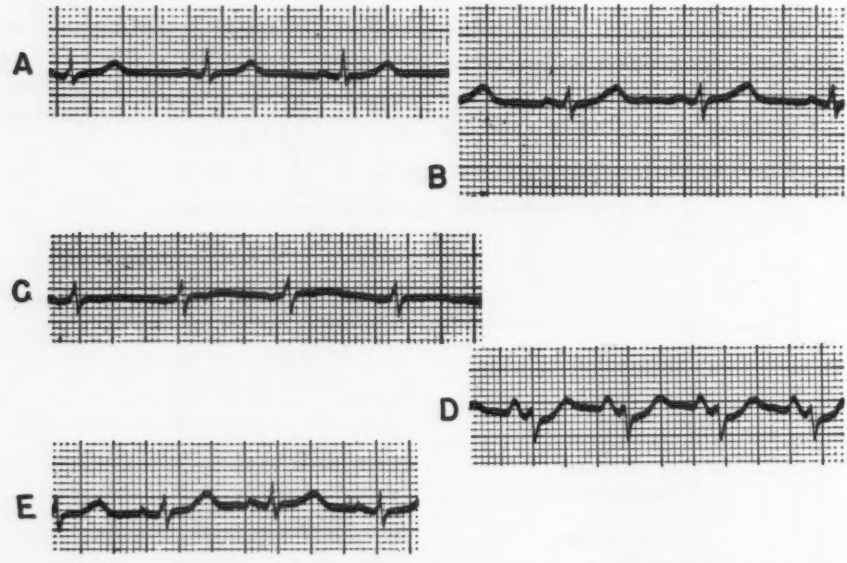

FIGURE 5 (all lead 2); A, before induction; B, following thiopental induction and 30 minutes nitrous oxide-Fluothane anaesthesia; C, 2 minutes after adrenaline injected with local–*P* and *T* wave depression; D, 5 minutes after adrenaline–*P* and *T* again upright, but *R* wave decreased in amplitude and *ST* segment depressed; E, 15 minutes later–return to pre-adrenaline tracing.

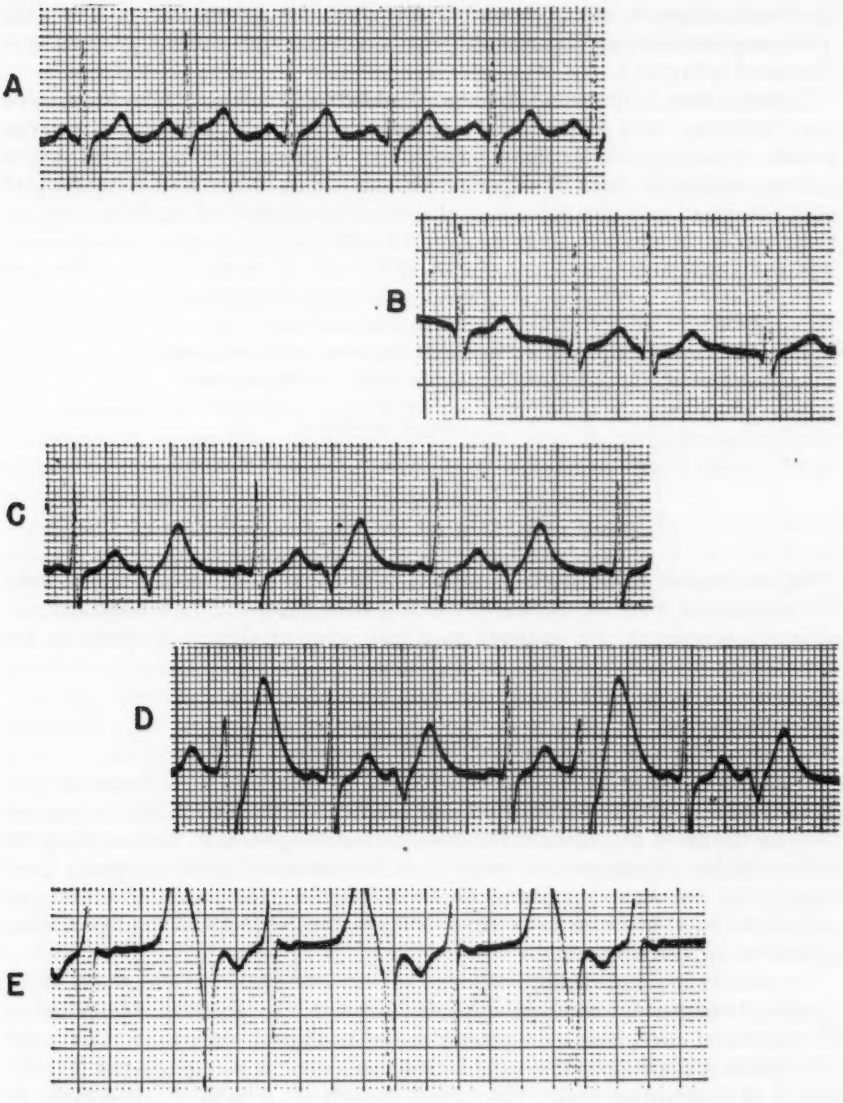

FIGURE 6: A, after induction–sinus rhythm; B, later–supraventricular extrasystole; C, 2 minutes after injection of local anaesthetic containing adrenaline–pulsus bigeminus; D, 10 minutes after injection–bigeminal rhythm with 2 alternating ventricular foci; E, 12 minutes after injection–bigeminal rhythm with single ventricular focus.

unrelated in time to the injection of adrenaline, are summarized in Table IX. A characteristic tracing demonstrating nodal rhythm with shifting pacemaker is illustrated in Figure 4.

The amount of l-adrenaline (free base) added to 125 ml. of 1/1500 Nupercaine was 500 microg.; most or all of this volume of solution was injected by the surgeon. Results obtained by the fluorimetric estimation of adrenaline in peripheral venous plasma, withdrawn from three patients ten to fifteen minutes after injection of local, are given in Table X.

TABLE X

ADRENALINE IN PERIPHERAL VENOUS PLASMA AFTER SUBCUTANEOUS INJECTION

	Before injection	10 min. after injection (microg. per litre)	45 min. after injection
1		0.39	
2	0.11	0.82	
3	0.21	0.67	0.15

Figure 5 traces the changes in cardiac conduction which occurred following the injection of local anaesthetic containing adrenaline. Figure 6 illustrates the changes observed in one patient, at a time when a definite increase in the circulating adrenaline level was demonstrable.

DISCUSSION

From this small series of patients subjected to Fluothane anaesthesia of light or moderate depth, several advantages which are difficult to dispute can be cited for the use of Fluothane in the anaesthetic management of the neurosurgical patient. These advantages are: swift, smooth induction; rapid emergence from anaesthesia; absence of respiratory tract irritation, with the attendant advantages of freedom from increases in cerebro-venous and cerebro-spinal fluid pressures; absence of explosive properties.

The smoothness and rapidity of induction and elimination of Fluothane invite superficial comparison with cyclopropane; however, the action of Fluothane on the peripheral circulation more closely resembles that of chloroform. The latter comparison is somewhat unfavourable, however, when it is remembered that the degree of hypotension during chloroform anaesthesia is usually proportional to depth of anaesthesia; with Fluothane this may not be the case. Hypotension is to be expected during Fluothane anaesthesia; it can occur with concentrations as low as 1 per cent; it frequently occurs in hypertensive patients; it may be difficult to control in the poor-risk patient; in certain patients hypotension may occur before a steady state of anaesthesia is attained.

There is little doubt that the occurrence of auricular fibrillation in one patient was closely related to existing hypotension of several minutes duration. It is

reasonable also to emphasize the danger of employing closed circuit anaesthesia with Fluothane unless vaporization can be accurately controlled independently of respiration.

At the levels of general anaesthesia employed for neurosurgery, distinctive changes in heart rate have not accompanied variations in blood pressure.

The duration of the operative procedures reported in this series provides a severe test of liver function; considerable increases in bromsulphalein retention occurred and have been attributed to Fluothane by other workers (5); but similar increases may accompany the administration of other anaesthetic agents, apart from the accepted effects of chloroform (8). In this series there was no clinical evidence of postoperative hepatic disturbance.

It appears, from the data obtained, that the cardiac effects of Fluothane do not greatly differ from those reported to occur during other forms of general anaesthesia (9). The effect on the heart of up to 500 microg. of adrenaline injected subcutaneously in conjunction with local analgesics must depend on the degree of absorption in unit time. Three patients in this series showed adrenaline levels within the range 0.39–0.82 microg. per litre of peripheral venous plasma 10–15 minutes after injection.

Although an extreme degree of accuracy cannot be claimed for the method of analysis employed, it appears from this that a definite increase in the circulating level of adrenaline is demonstrable following subcutaneous injection during surgical operations. Adrenaline levels below 1 microg. per litre are well within the range of values found in man and dogs during insulin hypoglycaemia (10) and during haemorrhagic shock in dogs (6).

In the laboratory animal experimental ventricular fibrillation is commonly induced by the intravenous injection of 10–20 microg./kg. of adrenaline, which must lead to precipitous increases in the plasma concentration of adrenaline to figures many times higher than those estimated in these three patients. Nevertheless, one of these patients showed, in sequence, supraventricular extrasystoles, pulsus bigeminus, and a multifocal bigeminal rhythm, within fifteen minutes of local injection, when the peripheral venous plasma concentration of adrenaline had risen to 0.82 microg. per litre from a pre-injection level of 0.11 microg.

Although three other patients showed ventricular extrasystoles after the injection of adrenaline, only one of these demonstrated recurring ectopic ventricular contractions.

From this limited evidence, it appears that the subcutaneous injection of adrenaline during uncomplicated Fluothane anaesthesia in man may be hazardous. The appearance in one patient of multifocal ventricular extrasystoles emphasizes the potentially dangerous situation which arises when even a moderate degree of anoxia occurs during Fluothane anaesthesia; nor can the possible role of injected adrenaline in this patient be underestimated. Further data is required.

The use of Fluothane can be recommended unreservedly for diagnostic radiological procedures, a field in which this new agent appears to be superior to trichlorethylene.

The difficulty presented by hypotension induced by Fluothane may be overcome by more comprehensive experience, but peripheral circulatory depression is

the most serious impediment to unconditional acceptance of Fluothane at this time. If hypotension can be utilized and controlled with the aid of carefully administered vasopressor drugs, the potentialities of Fluothane in neurosurgical anaesthesia increase.

Summary

The volatile anaesthetic agent, Fluothane, has been employed for 108 neurosurgical procedures.

The non-irritant, non-explosive properties of Fluothane, together with a desirable flexibility in action, render it a potentially valuable agent for the anaesthetic management of the neurosurgical patient.

A serious disadvantage of Fluothane derives from its hypotensive action, which may appear before an adequate level of anaesthesia has been attained.

There is electrocardiographic evidence that the combination of Fluothane and subcutaneously injected adrenaline is a potential hazard in man.

Tests of liver function after prolonged operations reveal definite abnormality, but this may not be greater than it would be with other anaesthetic agents administered and studied under similar conditions.

Fluothane deserves continued investigation as a promising new agent for major neurosurgical procedures. At the present time, its use can be particularly recommended for neuro-radiological investigations under general anaesthesia.

Acknowledgments

Many have aided in this study, the authors would like especially to express their gratitude to Doctors J. A. Shanks, A. J. Johnson and Ivan Beck for their clinical advice, and to their residents, Doctors I. Hildebrand and E. Osmolski for technical help.

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Résumé

Nous avons utilisé un agent anesthésique volatile, le Fluothane, au cours de 108 interventions neurochirurgicales.

Les propriétés non-irritantes et non-explosives du Fluothane jointes à une grande maniabilité et à son action rapide en feront peut-être un précieux agent anesthésique en neurochirurgie.

Il a cependant le sérieux désavantage de présenter fréquemment une action hypotensive qui peut apparaître avant même qu'un niveau suffisant d'anesthésie ne soit atteint.

Les tracés électrocardiographiques nous font également soupçonner que l'usage du Fluothane en combinaison avec l'injection sous cutanée d'adrénaline peut avoir un effet nuisible sur le myocarde.

Les épreuves de fonction hépatique après des interventions prolongées se sont montrées nettement anormales dans environ un tiers des cas, mais ces troubles ne semblent pas être plus sérieux que ceux que produisent d'autres agents anesthésiques administrés et étudiés dans les mêmes conditions.

Les avantages du Fluothane méritent certainement que l'on poursuive plus loin les recherches mais pour le moment son emploi paraît être plus particuliérement indiqué dans l'anesthésie générale au cours des examens neuro-radiologiques.

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HEART SOUNDS DURING FLUOTHANE ANAESTHESIA*

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and RALPH M. TOVELL, M.D.

THE RECENT INTRODUCTION of Fluothane ($CF_3CHClBr$) as an anaesthetic agent has prompted great clinical interest. Considerable enthusiasm has been evoked because this drug is a potent inhalational agent which is non-explosive, non inflammable, and provides a rapid induction of, and recovery from, anaesthesia (1, 2, 3, 4). Fluothane, however, is not without certain undesirable characteristics, as might be anticipated on the basis of previous experiences with other halogenated hydrocarbon compounds employed for anaesthesia. Some of these properties have been observed during clinical trials conducted in the present series of 125 patients anaesthetized with Fluothane. Depression of the tidal volume of respirations, to as low as 50 cc., 75 cc., or 100 cc., with the concurrent onset of tachypnoea, has occurred with considerable regularity when respirations have not been either assisted or controlled; hypotension, occasionally profound, has resulted without warning in several instances; and cardiac irregularities, consisting of either premature ventricular contractions or nodal rhythms, have been recorded on the electrocardiogram in 8 of the 125 patients who were anaesthetized with Fluothane. These unpleasant effects usually have occurred as the result of increasing depths of anaesthesia, and often have been reversible when the level of anaesthesia has been lightened again.

The depth of anaesthesia produced by a given concentration of inhaled Fluothane vapour, however, varies with the individual patient, and cannot always be judged adequately by clinical signs. The safety of widespread usage of Fluothane anaesthesia will have to be predicated upon reliable methods of ascertaining the depth of anaesthesia if these deleterious toxic effects are to be avoided. Calibration of the vaporizer by which the anaesthesia is to be administered provides considerable aid in determining the approximate anaesthetic level, but is not an infallible method in view of the sudden changes in the concentration of the vapour of this extremely potent agent that may result from alteration in the volume of even several inhalations. Determinations of the level of the agent in the arterial blood would provide definitive information, but these tests are technically difficult to perform and in any event cannot give immediate results for use in the conduct of clinical anaesthesia. Electroencephalography will provide minute-to-minute data for the control of the level of anaesthesia, but monitoring apparatus of this type is still not available to the majority of anaesthesiologists. The present study was therefore undertaken as an attempt to develop a practical and simple clinical method for monitoring Fluothane anaesthesia.

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TECHNIQUE

The changes that occur in the heart sounds during anaesthesia produced by either cyclopropane or ether have been reported by Rence, Cullen and Hamilton, (5) who observed that during deep levels of anaesthesia the usual predominance of the intensity of the first heart sound over the second heart sound became reversed, the second heart sound becoming greater relative to the first. These workers employed an Electron-cardioscope to demonstrate and record the heart sounds simultaneously with cathode-ray tracing, and sound-tape analysis was then done with camera and sound spectrograph. Their observations have been confirmed in the present study, which has employed phonocardiography and an optical recording system. Excellent tracings of the heart sounds during anaesthesia can be recorded by this means and have shown that the "reversal" of the two

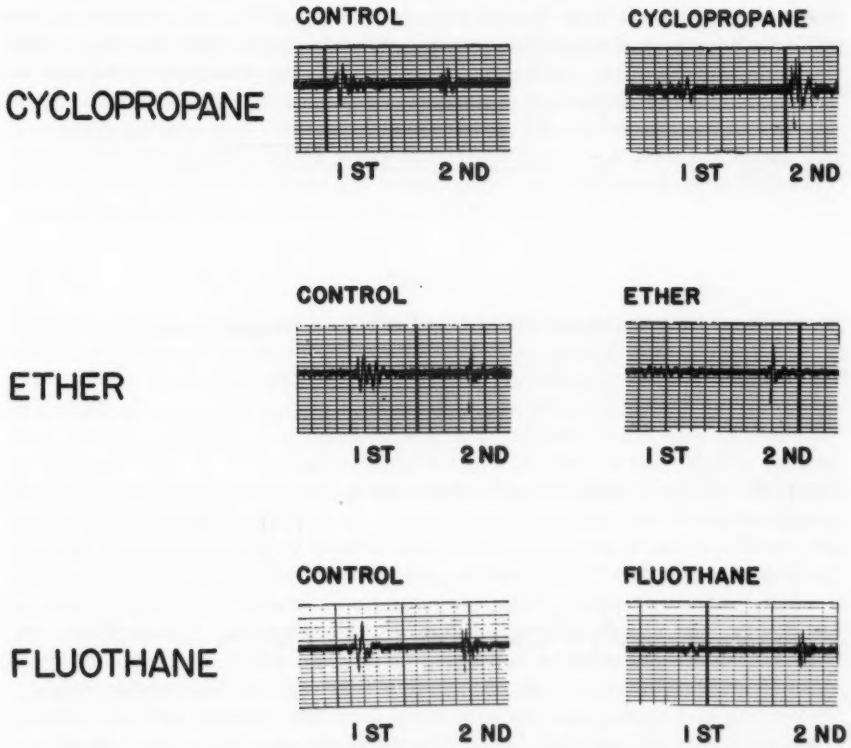

FIGURE 1. Heart sound "reversal" during anaesthesia. The upper tracings show the amplitudes, frequencies, and durations of the heart sounds of a patient before operation (control) and during cyclopropane anaesthesia. The middle tracings show similar records of a patient anaesthetized with ether, and the lower tracings are those from a patient anaesthetized with nitrous oxide–oxygen–Fluothane.

major heart sounds occurs not only with cyclopropane or ether, but also during anaesthesia produced by Fluothane (Fig. 1). Rence, Cullen and Hamilton made the suggestion that the changes in the heart sounds might serve as a qualitative guide to the determination of the anaesthetic level during cyclopropane or ether anaesthesia, and the fact that similar changes have been observed during Fluothane anaesthesia indicated that monitoring the heart sounds might also provide a guide to the safe dosage of Fluothane.

Methods and Material

An attempt therefore has been made to utilize the "reversal" of heart sounds during Fluothane anaesthesia as a practical determination of anaesthetic level and as an indication of the approach to toxic doses. The subjects were fifteen patients undergoing gynaecological surgery, all of whom were in good health except for the pelvic disorder for which operation was being undertaken. Anaesthesia was produced with the semi-closed technique by nitrous oxide–oxygen (6 litres: 3 litres) and Fluothane, occasionally with a small (100–200 mgm.) dose of thiopentone for induction. Heart sounds were monitored aurally by an acoustic stethoscope and an amplifying stethoscope, both applied to the precordium; and

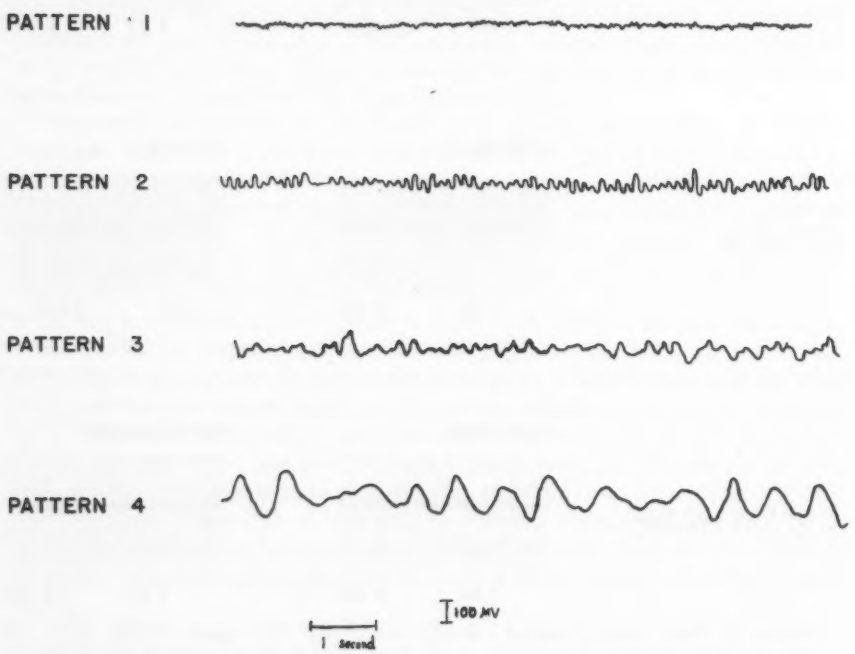

Figure 2. The electroencephalographic tracings recorded from fronto-occipital leads on a subject anaesthetized with nitrous oxide–oxygen–Fluothane. Below the tracings are scales indicating the time interval of one second and the amplitude of 100 μV.

visually by a cathode ray oscilloscope. Simultaneous phonocardiograms and electrocardiograms were recorded intermittently as indicated on a Sanborn Twin-Beam optical recorder (Model 62). Electroencephalograms were recorded on an Edin Anesthograph (Model 555). Blood pressures were taken with a cuff sphygmomanometer. The inhaled concentration of Fluothane vapour was recorded in terms of the setting on the Heidbrink ether vaporizer (that is, setting of 2.0 = 1.8 per cent inhaled concentration at the flow rates of gases employed in this study).

The depth of anaesthesia was estimated by reference to the electroencephalographic pattern pertaining at any given moment. Four electroencephalographic levels were discerned during anaesthesia produced by Fluothane, all similar to the patterns produced by different levels of other anaesthetic agents. The tracings of a subject anaesthetized with nitrous oxide–oxygen–Fluothane (without Pentothal induction or surgical intervention) is illustrative of the levels of anaesthesia as determined by electroencephalography in the present study (Fig. 2). The first pattern is characterized by low voltage, fast activity at 8–12 cycles per second; clinically, this corresponds to definite, but very light, Fluothane anaesthesia. The second pattern consists of waves of a higher voltage and a somewhat slower frequency of 6–8 cycles per second, in which the wave form is remarkably pure. The third pattern is a mixture of fast activity, of similar voltage to the preceding pattern, superimposed upon slow frequency, high voltage waves. The fourth pattern is characterized by almost pure delta waves of slow frequency, 2–4 cycles per second, and high voltage, 100–300 μv.

Results

The results are contained in Table I which lists the concentration of inhaled Fluothane vapour (as indicated by the vaporizer setting with a fixed flow of gases), the electroencephalographic pattern (according to the classification described above), the electrocardiographic changes, the blood pressure, and the type of respiration, for each of the fifteen subjects at the time of "reversal" of the heart sounds. The heart sounds did not, in fact, reverse in four patients (M. B., A. G., R. C., and E. A.), despite high concentrations of inhaled Fluothane vapour (for example, patient E. A., vaporizer setting=5.0) and electroencephalographic evidence of a deep level of anaesthesia (patterns 3 and 4). There was no correlation between the concentration of the inhaled Fluothane vapour and changes in the heart sounds: "reversal" occurred at a vaporizer setting of 1.0 in three patients, 1.5 in one patient, 2.0 in three patients, 2.5 in one patient, and 3.0 in three patients. There was also no correlation between the electroencephalographic pattern and changes in the heart sounds: "reversal" occurred during pattern 1 in four patients, pattern 2 in six patients, and pattern 3 in one patient. An approximate correlation could be established between the concentration of the inhaled Fluothane vapour and the electroencephalographic pattern in most instances, the lower vaporizer settings (1.0 to 2.0) producing electroencephalographic patterns 1 or 2, and the higher vaporizer settings (3.0 to 5.0) producing electroencephalographic patterns 3 or 4. There was no correlation between

"reversal" of the heart sounds and the level of systolic arterial pressure, which was normal in nine of the eleven patients showing such a change in heart sounds, and in three of the four patients in whom the heart sounds did not reverse throughout the anaesthetic period. There also was no relation between the effects of Fluothane upon either the type of respiration or the pulse rate and the occurrence of "reversal" of the heart sounds.

TABLE I

PHONOCARDIOGRAPHIC "REVERSAL"* OF HEART SOUNDS CORRELATED WITH CONCENTRATION OF INHALED FLUOTHANE VAPOUR, ELECTROENCEPHALOGRAPHIC PATTERN, ELECTROCARDIOGRAM, BLOOD PRESSURE AND RESPIRATIONS

	Observations at time of "reversal" of heart sounds				
Patient	Vaporizer setting	EEG pattern	ECG	Blood pressure	Respirations
R.C.	3.0	2	Normal	Normal	Assisted
M.V.	2.5	2	Normal	Normal	Normal
M.B.	No "reversal" @ 3.0	No "reversal" @ 3	Normal	Normal	Normal
K.G.	1.0	1	Normal	Normal	Normal
B.C.	1.5	2	Normal	Normal	Normal
B.L.	1.0	1	Normal	Normal	Normal
C.V.	2.0	2	Bradycardia	Depressed	Assisted
A.G.	No "reversal" @ 3.0	No "reversal" @ 3	Normal	Normal	Normal
E.N.	1.0	1	Normal	Normal	Normal
L.K.	2.0	2	Normal	Normal	Normal
R.C.	No "reversal" @ 5.0	No "reversal" @ 4	Normal	Normal	Normal
C.M.	3.0	3	Bradycardia	Normal	Assisted
S.O.	3.0	1–2	Normal	Normal	Normal
E.A.	No "reversal" @ 2.5	No "reversal" @ 3	Bradycardia	Depressed	Controlled
M.C.	2.0	2	Normal	Depressed	Controlled

*"Reversal" refers to a change from the usual predominance of the 1st heart sound over the 2nd, to a predominance of the 2nd heart sound over the 1st, as described in the text.

DISCUSSION

Four heart sounds can be recorded by phonocardiography, but the first and second sounds (6), which signify the beginning and end of systole respectively, are louder and more commonly heard than the diastolic sounds, the third and fourth heart sounds (7). The first heart sound is of relatively long duration, low in pitch, and soft in quality, and is caused by complex musculo-valvular mechanisms which have been hypothesized to include the closure of the auriculoventricular valves, the tension set up in the valve leaflets and chordae tendinae as the intraventricular pressure rises, the rush of blood from the ventricles and the shock transmitted to the walls of the aorta and pulmonary artery, the contraction of the ventricular muscle, and vibrations set up by the auricular muscle at the end of its systole (8). The intensity of the first sound is related to the tension developed during the isometric phase of ventricular contraction (9). The second sound is shorter, sharper, and of higher pitch, and results from the vibrations set up in the column of blood and arterial

walls coinciding in time to the closure of the semilunar valves and the subsequent opening of the atrioventricular valves (7). The intensity of the second heart sound is related to the height of blood pressure in the great vessels at the onset of diastole (9).

The changes in the heart sounds during deep anaesthesia produced by either cyclopropane or ether were attributed by Rence, Cullen and Hamilton (5) to a depression of cardiac action, indicating low energy output and tending to suggest a direct cardiotoxic action. This concept that the changes in heart sounds are due to a decrease in the contractile force of the heart may well pertain to the data in the present study, but the effects of hypoxia, hypercarbia, and particularly surgical stimuli could not be sufficiently controlled to warrant such a conclusion. It is of interest, in this regard, that "reversal" of the two major heart sounds were not seen during anaesthesia produced by nitrous oxide–succinylcholine or during induced hypothermia to a temperature of 86°F. in human patients (10).

Changes in the heart sounds during Fluothane anaesthesia were discernible on the oscilloscope when they did occur, but were not always distinguishable by acoustic stethoscope until the "reversal" was pronounced. Furthermore, an equalization of the first and second heart sounds generally occurred prior to true "reversal," which was noted slightly later when the second sound became predominant. There is therefore a disparity between the results in this study of Fluothane and the findings of Rence, Cullen and Hamilton that "reversal" occurred with ether or cyclopropane before the sounds assumed an equality of pitch and intensity (5).

Conclusions

1. The usual predominance of the intensity of the first heart sound over that of the second heart sound frequently may be reversed during anaesthesia produced by Fluothane, the intensity of the second heart sound becoming greater relative to the first heart sound.
2. Four electroencephalographic patterns were discerned during anaesthesia produced by Fluothane, and a good correlation could be shown to exist between these patterns and the concentration of the inhaled vapour of Fluothane in most instances.
3. No constant correlation could be defined between the changes in the heart sounds and either the concentration of the inhaled vapour of Fluothane or the electroencephalographic patterns produced by this drug.
4. Preliminary attempts to employ the changes in heart sounds during Fluothane anaesthesia as a guide to anaesthetic depth have been unsuccessful.

Résumé

Nous avons donné l'anesthésie à 125 malades avec un dérivé ethane nouveau-venu: le Fluothane ($CF_3CHClBr$); chez huit de ces malades, nous avons dépisté des contractions ventriculaires prématurées ou un rythme nodal. Ces effets

nuisibles sur le cœur de l'anesthésie au Fluothane, nous les avons attribués soit à un surdosage de l'agent anesthésique, soit à de l'hypoventilation malgré toutes les précautions prises pour éviter celle-ci en recourant à la respiration assistée et même à la respiration contrôlée.

Nous avons noté le fait que les bruits cardiaques étaient fréquemment inverses au cours de l'anesthésie au Fluothane et nous avons pensé qu'en amplifiant ces bruits nous pourrions les employer comme indices de la profondeur de l'anesthésie et moniteurs de l'imminence de la toxicité cardiaque. Alors nous avons enregistré simultanément des phonocardiogrammes et des électrocardiogrammes sur un Sanborn Twin-Beam Optical Recorder et des électroencéphalogrammes sur un anesthésiographe Edin (model 555) avant et pendant l'anesthésie au Fluothane chez 15 malades soumises à de la chirurgie gynécologique. Nous avons essayé d'établir une relation entre les changements dans les bruits du cœur et la profondeur de l'anesthésie telle qu'indiquée par les tracés électroencéphalographiques et/ou la concentration des capeurs de Fluothane inhalées.

Comme résultats, nous avons réalisé que les bruits cardiaques ne sont pas toujours inverses au cours de l'anesthésie au Fluothane; et, par contre, cette inversion peut survenir précocement au cours de l'administration de l'anesthésie. Nous n'avons pas pu établir de relation constante de cette inversion ni avec la concentration des vapeurs de Fluothane inhalées ni avec le tracé électroencéphalographique enregistré au cours de cette anesthésie, bien qu'il soit possible d'en établir une, dans la plupart des cas, entre la concentration des vapeurs inhalées et les tracés électroencéphalographiques. Nous en arrivons à la conclusion que, bien que l'inversion des bruits cardiaques apparaisse fréquemment au cours de l'anesthésie au Fluothane, il n'est pas possible d'utiliser cette inversion comme signe clinique de la profondeur de l'anesthésie.

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AN ATTEMPT TO CORRELATE THE CLINICAL SIGNS OF FLUOTHANE ANAESTHESIA WITH THE ELECTROENCEPHALOGRAPHIC LEVELS

E. A. Gain, M.D., and S. G. Paletz, L.R.C.P.*

Recently, rather enthusiastic reports (1, 2, 3, 4) concerning Fluothane (CF_3 CHCl Br) appeared in the literature. The published reports (1, 2) indicated that this was an exceedingly potent, non-irritating, non-explosive agent, requiring careful control of concentration and easy recognition of anaesthetic depth if over-dose and resulting serious cardiovascular depression were to be avoided. Since few anaesthetists have available at present the facilities for constant accurate control of concentration, it seemed necessary to find dependable easily recognised clinical signs, and to correlate these with the accurate electroencephalographic levels. In this way a satisfactory safe pattern of anaesthesia would be available.

Method

Twenty-two unselected patients were studied. The type of operation, age range and duration of anaesthesia were as follows.

Type of Operative Procedures

Gynaecological: dilatation and curettage, 3; abdominal hysterectomy, 1.

Genito-urinary: cystoscopy, 1; nephrectomy, 2; ureterolithotomy, 1.

Abdominal: cholecystectomy, 1; colon resection, 1; gastrectomy, 2; appendectomy, 1; herniorrhaphy, 2.

Ophthalmological: ptosis repair, 1; recession and resection, 1.

Neurosurgical: Exostosis skull, 1; skull defect, 1; plastic skin graft, 1.

Trunk: Breast biopsy, 2.

Age range: 6 months to 72 years.

Anaesthesia time: 20 minutes to 225 minutes.

All patients received standard meperidine and atropine premedication except two, who received only standard atropine. Induction was accomplished with thiopental and succinylcholine or nitrous oxide–oxygen–Fluothane or open drop Fluothane. Maintenance was with nitrous oxide (2 litres) and oxygen (2 litres) in a semi-closed circle absorption system, using a No. 8 Heidbrink vaporizer and a No. 9 B absorber. The two patients receiving open drop Fluothane were maintained by the open drop technique.

The flowmeters on this anaesthetic machine had been previously tested and found to be accurate. Gas analysis was not considered necessary. Similarly previous tests had shown that with controlled respiration there was an absence of hypoxia and hypercarbia.

An Edin Anesthograph with fronto-occipital scalp leads and the standard lead II electrocardiograph were attached and recording commenced before induction and continued thereafter throughout the procedure.

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Previous reports of rapid induction, quiet respiration, excellent relaxation, rapid recovery and low incidence of nausea and vomiting were soon confirmed.

A Bennett ventilation meter showed that in every instance of surgical anaesthesia tidal exchange was decreased necessitating assisted respiration, except when the pattern of repiration was being specifically observed. Assisted respiration always became controlled respiration, often even in Level I (E.E.G.) anaesthesia.

Electroencephalographic Pattern

The Edin Anesthograph used has a frequency response of 1 to 30 cycles per second. The sensitivity was such that 100 microvolts input gave a one centimetre deflection. The chart speed was 15 millimetres per second. The patterns obtained were all interpreted by one of us (S.G.P.) and a representative series is illustrated in Figure 1. The interpretations are as follows:

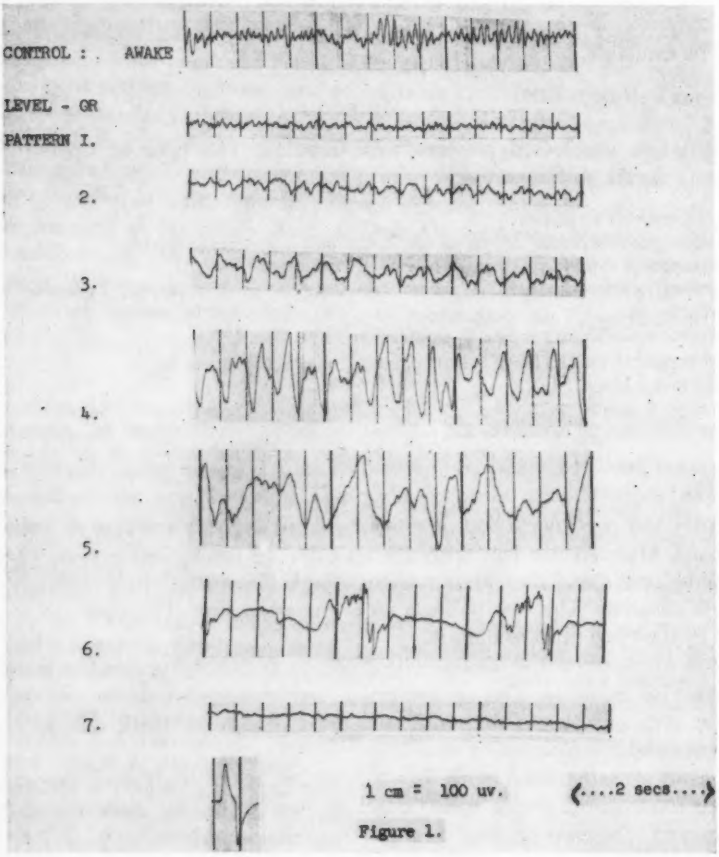

Figure 1

Control awake: the normal alpha rhythm of 10 to 12 cycles per second with an amplitude of 25 to 50 microvolts.

Pattern or Level I: a fast frequency with a low voltage; the frequency ranged from 15 to 25 cycles per second and the amplitude from 10 to 25 microvolts.

Pattern 2: very low voltage fast activity superimposed on slow waves with a moderate voltage; the slow waves range from 3 to 6 cycles per second with an amplitude of 50 microvolts.

Pattern 3: the superimposed low voltage fast activity is disappearing; the slow waves have increased in amplitude whilst decreasing in frequency; they are 4 cycles per second with an amplitude of 50 to 100 microvolts.

Pattern 4: the fast activity has disappeared leaving only slow waves with a frequency of 2–3 cycles per second and an amplitude of 100 to 300 microvolts; many of these slow waves are notched and irregular.

Pattern 5: the slow waves are now one per second with an amplitude of 100 to 200 microvolts; superimposed on these slow waves and appearing between them are waves with a frequency of 6 to 8 cycles per second with an amplitude of 25 to 50 microvolts.

Pattern 6: the frequency is now one wave every 2 to 3 seconds; this wave has an amplitude of 200 microvolts; the superimposed and interposed 6 to 8 cycles per second waves have a reduced amplitude of 25 microvolts; this is the first appearance of a burst suppression of cortical activity.

Pattern 7: there is now no cortical electrical activity for an extended period; a complete absence of any wave form.

When anaesthesia is lightened, the electroencephalographic patterns are reproduced; this occurs rapidly.

Clinical Signs

Consciousness. This was lost with the definite establishment of Level I.

Eye signs. The eyelid reflex disappeared in Level I. Eyeball oscillation usually disappeared in Level II, but sometimes in Level I. Pupils remain constricted until the deepest levels when they dilate. Lacrimation persisted into Level II.

Respiratory signs. These resembled those of cyclopropane. Spontaneous apnoea occurred in Level IV. A progressive intercostal paralysis occurred, but often this was too rapid to be appreciated. As noted, respiration was easily controlled at any level. At surgical levels the rate was moderate to slow but became rapid from stimulation in Level I. Premedication undoubtedly has considerable influence on the respiratory signs but this was not investigated.

Cardiovascular signs. The pulse rate is not a constant predictable sign. Usually it remained constant until Level III, when a bradycardia occurred. However bradycardia occurred as early as Level II and as late as Level IV. Often bradycardia was noted only in the presence of severe hypotension. Occasionally a relative tachycardia accompanied severe hypotension.

The blood pressure falls with induction returning to near preanaesthetic levels soon after. As anaesthesia is deepened hypotension always occurs; usually above Level III the pressure remains satisfactory. There may be, and often is, a sudden dramatic severe hypotension in a matter of seconds, from what was previously a satisfactory pressure and light to moderate levels of anaesthesia. The E.E.G. then records Levels V, VI, or VII.

We noted that the systolic pressure was not recordable by clinical methods

in most cases from Level V downward. Often the precipitous disappearance of the blood pressure is striking. The electrocardiograph showed electrical activity through all levels, although in the deeper levels there was a diminution of voltage. A carotid pulse was always palpable. Cardiac arrhythmias occurred in six patients, and showed no relation to depth of anaesthesia or method of ventilation. The irregularities occurred in patients under controlled respiration disagreeing with Johnstone's (1) report that irregularities are only associated with inadequate ventilation. One further patient was receiving open drop Fluothane and so was undoubtedly hypercarbic.

A wide variety of *arrhythmias* occurred: isolated ventricular extrasystoles (2 cases), pulsus bigeminus (1 case), ventricular tachycardia (1 case), nodal rhythm (1 case), and the peculiar sinus coupling (1 case), described by Johnstone (1). These arrhythmias were not always rapidly reversed by lightening the anaesthesia and maintaining excellent ventilation. The sinus coupling persisted for six minutes and the ventricular tachycardia for three minutes. The frequent hypotension is reversible by atropine in levels up to III, but not at deeper levels. No attempt was made to correct hypotension with vasopressors.

Muscle relaxation. This occurs early. Level III was necessary for endotracheal intubation. The limbs are relaxed in Level II. Abdominal relaxation is usually satisfactory in Level III. With controlled respiration relaxation is adequate in Level II and in the elderly patient, Level I proved adequate. Muscle relaxants were not used except for endotracheal intubation, and then only depolarisers.

Response to pain. Level II was sufficient for extra-abdominal procedures. Peritoneal traction often necessitated Level III, especially when respiration was not controlled.

Skin is usually warm and dry throughout all levels. Perspiration may occur in Level I and II if stimulation is intense. The flush described has not been noted in this study.

Discussion

From this small clinical study we agree with most of the reports. We gained the impression that Fluothane is a primary respiratory and cardiac depressant. The bradycardia and hypotension appear to be the result of direct myocardial depression, as much as the suggested sympathetic block (1). It is rare to see such profound circulatory collapse in young robust males (as we have produced with Fluothane) with ganglionic blockers. This profound collapse can occur in the time required for a few inspirations, reminiscent of chloroform.

Robson and Sheridan (4), using vasopressors to support the circulation during deepening anaesthesia, have shown comparative E.E.G. patterns. This was not attempted by us. No attempt was made to correct hypotension with vasopressors. We do not consider vasopressors advisable in hypotension which may be due to myocardial toxicity, a possiblity which has not yet been excluded with Fluothane. Rapid washout of the agent produced satisfactory pressures and was considered safer.

Conclusion

An attempted study to correlate the clinical signs of Fluothane anaesthesia with the E.E.G. patterns has been presented. The deeper E.E.G. patterns may have been influenced by the circulatory collapse which always occurred. This may also have contributed to the dilated pupils previously mentioned. We were unable to elucidate clear, concise or safe, clinical signs to guide one in the administration of Fluothane, without causing cardiovascular and respiratory depression. Whether this depression is significant has to be established. We cannot agree with Bryce-Smith (2) who suggests that Fluothane may be a useful agent for the general practitioner, or with Johnstone (1) who suggests that this agent has a high cardiac safety factor. A great deal of study must go into this agent before it can be properly evaluated. We cannot at present recommend the general use of this agent.

Summary

An attempt was made to present the electroencephalographic patterns of Fluothane anaesthesia and to correlate these patterns with the clinical signs of anaesthesia. This could not be done as there were no reliable clinical signs present. The lower electroencephalographic patterns presented are open to question, as the profound circulatory collapse which always occurred at these levels may have influenced them. A high incidence of dangerous cardiac arrhythmias were noted. Respiratory depression was prominent. The authors believe that Fluothane is a myocardial depressant resembling chloroform. We suggest that Fluothane should not be made available for general distribution until safe proven methods of administration are developed.

Résumé

Tentative d'établir une corrélation entre les signes cliniques d'anesthésie au Fluothane et les tracés électroencéphalographiques

Nous avons essayé d'étudier les tracés électroencéphalographiques enrégistrés au cours de l'anesthésie au Fluothane et d'établir une relation entre ces tracés et les signes cliniques d'anesthésie. Nous n'avons pas réussi car nous n'avons pas observé de signes cliniques fiables. Les tracés électroencéphalographiques des plans plus profonds sont douteux car le collapse circulatoire important qui accompagne inévitablement ces plans peut influencer les tracés. Nous avons observé une grande incidence d'arythmies cardiaques dangereuses. La dépression respiratoire a été manifeste. Les auteurs ont l'impression que le Fluothane produit une dépression myocardique ressemblant à celle que produit le chloroforme. Nous suggérons que le Fluothane ne soit pas mis à la disposition de tous avant que des méthodes d'administration de toute sécurité soient mises à point.

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THE PHYSIOLOGICAL EFFECTS OF INTRAVENOUS ANAESTHESIA ON MAN

ALLEN B. DOBKIN, M.D., and GORDON M. WYANT, F.F.A.R.C.S.*

INTRODUCTION

KEATING noted in 1956 that intravenous anaesthetics cause as many sudden unexplained deaths as did chloroform (1). From recent extensive reviews it appears that estimated death rates from intravenous anaesthetics have been conservative (2, 3, 4). The introduction of new or "better" intravenous agents must therefore be most carefully assessed in the most reliable and valid parameters available for study.

Theory and data recently procured have provided the clinical anaesthetist with some fundamental facts which should form a basis for comparing new agents and for the improved management of intravenous inductions of anaesthesia.

First, and foremost, the effect of premedicant drugs administered to the patient before the intravenous anaesthetic agent must be determined. For this reason, all drugs tested should be given preferably to unpremedicated subjects in order to separate the changes in vasomotor and haemodynamic stability as well as in respiration which occur with premedicant drugs. Clinicians have almost totally ignored or have not included these effects in their studies of changes (5–11).

In addition to theoretical considerations of the intrinsic activity of each drug, the affinity of drugs for various tissues and the effect of drug interaction, it is essential that the anaesthetist also note the physiological age, the state of nutrition and hydration as well as the state of electrolytes in the subjects whom he studies.

To compare the effects of drugs under clinical tests in a group of patients in whom the above factors vary widely is completely invalid. To procure the usual average series of unselected cases may merely add to the variability of the basic conditions and throw in the less common disturbing factors of varying sensitivity.

Other factors of vital concern, particularly with respect to the ultra-short acting intravenous agents, are the phenomena of cumulation, of acute tolerance,

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Supplies of drugs were kindly made available by the following firms: sodium thiopental (Pentothal®) by Abbott Laboratories, Montreal, P.Q.; thiamylal sodium (Surital®) by Parke, Davis and Company Ltd., Walkerville, Ontario; hexobarbital sodium (Evipal®) by Winthrop Stearns Inc., New York; methitural sodium (Neraval®) by Schering Corporation, Montreal, P.Q.; buthalitone sodium (Transithal®) by Poulenc Ltd., Montreal, P.Q.; Compound 25398 by Eli Lilly and Company, Indianapolis, Ind.; and MRD-125 (Dolitrone®) by the Wm. S. Merrill Company, Cincinnati, Ohio, U.S.A.

The Wm. S. Merrill Company, Poulenc Ltd., Schering Corporation and Abbott Laboratories assisted in this study by a grant-in-aid.

and perhaps also of tachyphylaxis. Since the intravenous anaesthetics reach a very rapid peak of concentration sequentially in the blood, the brain, and the heart, at a rate which is almost synchronous with the circulation time, and then are rapidly redistributed to the rest of the body, the effect of this initial distribution must be evaluated when several drugs are to be compared. This evaluation is very imporant, because the cerebral blood flow is maintained even when a state of shock is impending or present. Therefore, the effect of intravenous dugs on the brain will vary in an inverse relationship to the cardiac output. Subsequent injections of a drug under test produce a greater effect on the central nervous system and a lesser effect on the haemodynamics and cannot provide a valid comparison. The cumulative effects or tachyphylaxis further confuse this picture.

As for the phenomenon of *acute tolerance,* Dundee and his associates have shown that the awakening time from intravenous anaesthesia (thiopental) is primarily determined by the initial or acute dose of the intravenous anaesthetic (12).

The physiological effect of intravenous anaesthetic agents on haemodynamics must be considered of primary importance to the clinical anaesthetist, for a large proportion of deaths attributable to inductions of intravenous anaesthetic are caused by both respiratory and cardiovascular depression. The respiratory depression is quite easily supported, while the cardiovascular depression frequently cannot be reversed by vasopressors, by atropine and other supportive measures, especially in elderly or debilitated patients. As many new agents are becoming available, it is essential to evaluate these carefully on healthy subjects prior to employing them in clinical trials. Since the greatest difficulties arise immediately after induction of anaesthesia, the most pertinent information should be obtained *at this time,* rather than after a so-called steady state develops. However these data are procured, the investigator must either account for the gross alterations from the basal state in the patient prepared for an operation or a test study, or clearly evaluate the effect of apprehension or of the narcotic premedication on the parameters being investigated.

One of the reasons for the paucity of data on the haemodynamic effects of anaesthetic agents is the technical difficulty encountered in procuring such information in man. Since a simple method was devised recently, it was deemed important to compare the effects of several intravenous anaesthetics on haemodynamics as well as on respiration of the *same individual subjects.* This comparison provided an integral part of the experimental and clinical evaluations of the newer anaesthetic agents which have been studied (13, 14).

Method

For each subject, vital statistics (sex, age, body build, height, weight and body surface area) were measured and noted. Blood volume fractions, venous haematocrit and resting vital signs were recorded. Respiratory and haemodynamic parameters were estimated and calculated from metabolism tables

INTRAVENOUS ANAESTHETICS

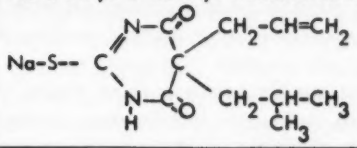
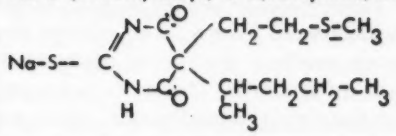
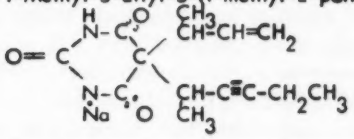
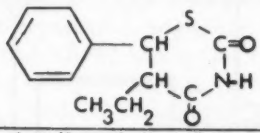
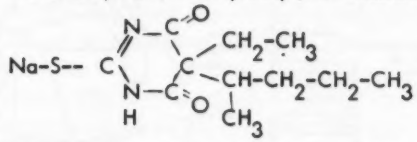
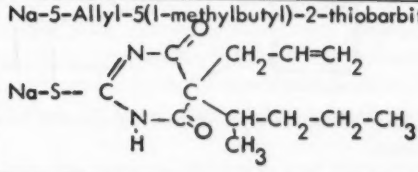
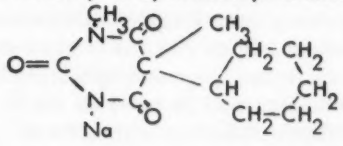
TRANSITHAL Na Buthalitone (Poulenc)	Na-5-Allyl-5-isobutyl-thiobarbiturate 
NERAVAL Na Methitural (Schering)	Na-5-(1-Methylbutyl)-5-2(methylthio) ethyl-2 thiobarbiturate 
Compound 25398 (Eli Lilly)	Na 1-Methyl-5-allyl-5-(1-methyl-2-pentynyl) barbiturate 
DOLITRONE (Merrill)	5-Ethyl-6-phenyl-M-thiazine-2,4-dione 
PENTOTHAL Na Thiopental (Abbott)	Na-5-Ethyl-5-(1-methylbutyl)-2-thiobarbiturate 
SURITAL Na Thi amylal (Parke-Davis)	Na-5-Allyl-5(1-methylbutyl)-2-thiobarbiturate 
EVIPAL Na Hexobarbital Winthrop-Stearns)	Na N-Methyl-5-cyclohexenyl-5-methyl barbiturate 

FIGURE 1. Comparative chemical structure of intravenous anaesthetics.

and from the nomograms of Radford and Jackson (15, 16). These data provided the base line for all changes recorded in the control period and in the acute and delayed test period. Alterations in recorded respiratory and haemodynamic parameters induced by apprehension or anxiety, and by the drugs under study, were then compared.

Data were obtained at weekly intervals from young, healthy, male subjects in a fasting state before and after intravenous administration of thiopental, thiamylal, hexobarbital, buthalitone, methitural, Compound 25398 and Dolitrone (Fig. 1). While the subject was requested to gaze at the ceiling, each freshly prepared drug was administered from a 20 ml. syringe in a 2.5 per cent solution through a 1½" 20-gauge needle at the rate of approximately 15 mg. per second until the eyelids closed involuntarily. Thereupon, an equal dose was injected as rapidly as pressure on the syringe would permit. Arrangement of recording data is shown in Figure 2.

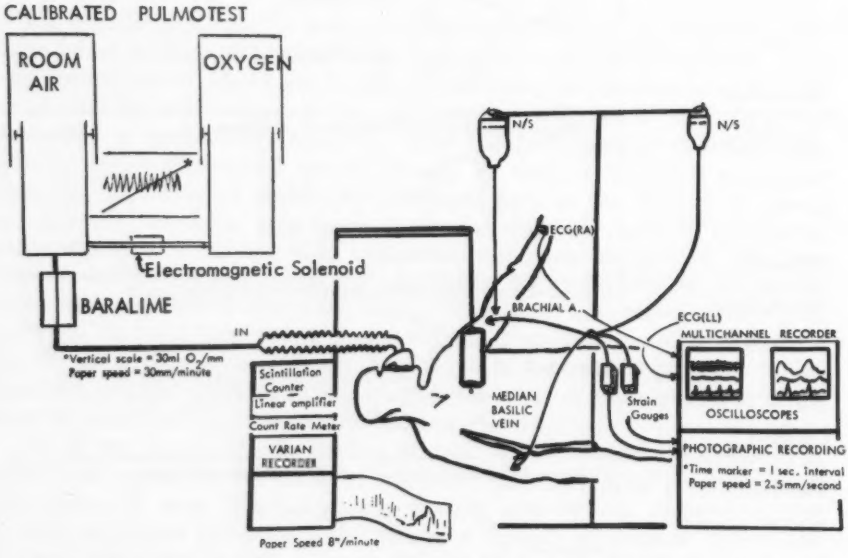


FIGURE 2. Arrangement of respiratory and haemodynamic recording equipment for study of intravenous anaesthetics.

As premedication was not given, it was realized that apprehension was the important factor in altering control values as compared to those of the resting state (17, 18). This could not be avoided even in trained human subjects. No attempt was made to record electroencephalographic levels, as these were virtually "acute" experiments, and in previous studies a grossly erroneous indication of anaesthetic depth and reflex responsiveness during intravenous anaesthesia was observed (13, 19). It was further evident that electroencephalographic levels are not comparable among anaesthetics, even when their route of adminis-

tration or mode of action may be similar. With any anaesthetic drug, if the "depth of anaesthesia" as determined by the electroencephalogram must be known within a reasonably steady blood level, collateral data must be obtained from repeated blood samples or a continuous monitor showing the arterial blood sugar, pO_2, pCO_2 and cerebral blood flow. Without this data, very wide variation in the blood level of the anaesthetic can exist, without significant alteration in the cortical potentials. Others are now beginning to report similar difficulties (20).

Determinations of blood volume were made on each subject prior to the drug tests, by means of a simple, accurate method which has been developed (21–25). Using human serum albumin iodinated with iodine^{131} and radioactive sodium chromate containing chromium^{51}, plasma volume and red cell volume were determined simultaneously (26, 27). In the first compound, the iodine is firmly bound to the protein and when injected intravenously, there is no transfer of activity to the plasma proteins or to the red cells. Since the albumin is physically and chemically almost identical to the ordinary serum albumin, there is only a slow leakage from the capillary bed. Evans Blue (T1824) diffuses relatively rapidly from the circulating plasma, and repeated determinations within short time intervals are not possible. In the Evans Blue method, lipaemia or haemolysis will cause interference, but since only radioactivity is being measured in the iodine^{131} serum albumin method, colour or turbidity is not a problem. When a highly sensitive well-type scintillation counter is used, the dose of radioactivity given to the patient is negligible. With sodium chromate (Na_2CrO_4) incubation with blood allows adsorption of the radioactive chromium^{51} by the cells and binding to the globulin in the cells. The calculation of plasma and red cell volume is based on the dilution principle, just as in the Evans Blue method. The general principles of this procedure are as follows:

1. (*a*) Venous blood (20 ml.) from the subject is added to 150 microcuries of chromium^{51} and allowed to incubate at room temperature. The subject's labelled cells are later reinjected.

(*b*) Iodine^{131} labelled albumin is diluted, using sterile containers and sterile saline to an activity level of about 5 microcuries per ml. Then, 5 to 10 microcuries of this dilution are injected intravenously into the subject, the syringe being well flushed with blood before being removed from the vein.

2. Standard dilute solutions are prepared by adding amounts exactly equal to that injected of the iodine^{131} and chromium^{51} to 4000 ml. and to 500 ml. volumetric flasks respectively and then bringing the solutions to the mark with distilled water.

3. Fifteen minutes after injection of iodine^{131} and chromium^{51} blood samples are withdrawn from the other arm and added to tubes containing heparin or a dried potassium-ammonium-oxalate mixture.

4. Haematocrit determinations are made on the blood and on an aliquot centrifuged to obtain about 3 ml. of plasma.

5. Then, 2 ml. samples of the standard solutions (2), the subject's blood (3) and plasma (4) are counted in a well-type scintillation counter.

6. After subtraction of background counts, a predicted blood volume may be estimated thus:

$$B.V. = \frac{\text{Plasma volume}}{1 - (\text{Hct} \times 0.9)}$$

and then may be calculated thus:

$$\text{Red cell volume} = \frac{\text{Counts per min. of injected solution/ml.}}{\text{Net counts/min./ml.}} \times \text{Volume of tagged cells injected}$$

$$\text{Plasma volume} = \frac{\text{Counts/min./ml. of standard}}{\text{Counts/min./ml. plasma}} \times \text{Volume of standard.}$$

Venous haematocrit was determined by centrifuging heparinized blood in Wintrobe tubes.

Normal values by this method in mg./kg. in 25 other subjects were as follows: red cell volume, 22 to 37 (mean 28.5 ± 4); plasma volume, 33 to 60 (mean 43.0 ± 6.8). Total blood volume ranged from 55 to 90. The ratio of body haematocrit to venous haematocrit in 108 estimations was 0.89 ± .05 (27).

Arterial and venous blood pressures were measured directly from the brachial artery and the median basilic vein through 5 cm. 18-gauge needles. These needles were connected to Statham strain gauges (Model P 23A) placed at the level of the right auricle, arbitrarily set at 100 mm. above the level of the back as recommended by Lyons and associates (28). These pressures together with lead 2 of the electrocardiogram were recorded continuously on two oscilloscopes with an infinite frequency response. One of these oscilloscopes was set to amplify the complexes. The pressure heads had a frequency response of 185 c.p.s. through a 5 cm. 20-gauge needle. Fry and associates have shown that the technical recording system employed is highly accurate and a stable system for recording pressure data (29). All tracings were photographed for permanent records and subsequent study.

The mean pulse rate, mean venous pressure, mean systolic and diastolic blood pressure and mean pulse pressures were computed from the average of all pulse rates and arterial and venous blood pressures measured on the tracings for each subject. These measurements were made in a representative three-minute period when other data were recorded (cardiac output, oxygen consumption, respiration rate and tidal volume) before and immediately after the injection of the test drugs and again for five to thirty minutes during the awakening period when blood pressure, pulse rate and respiration had stabilized somewhat. From the tracings the mean arterial blood pressure was computed thus: mean arterial blood pressure = mean diastolic B.P. + 1/3 (mean systolic B.P. − mean diastolic B.P.). It was found that this calculation provides essentially the same values as that determined by planimetry of the pulse waves.

Cardiac output. Cardiac output was measured by the recording of radioactivity transients at the precordium by the external body counting of iodine^{131} as described by Veall and associates in 1954 and by Huff and associates in 1955 (30, 31). The technique described by the latter authors was followed exactly. A collimator with a diameter of ¾ inch was used on a thyroid counter. The detector was placed over the skin between the first and second ribs at the left

parasternal line. The scintillation counter was connected to a count-rate meter and a Varian strip-chart recorder. For each determination 75 microcuries of Rihsa® in a small volume (1 ml.) were injected directly into the same median basilic vein in a single continuous motion at a rate not exceeding one second for the entire injection. The needle and vein were then flushed with normal saline. The uptake of Rihsa® was recorded until an equilibrium counting rate was observed on the calibrated recording chart. The initial fall in intensity of radioactivity following the first rise was extrapolated exponentially to the base line. The area under this curve was measured accurately by planimetry in square inches using a "Paragon" Compensating Polar Planimeter. The cardiac output in blood volumes per minute was then equal to:

$$\frac{\text{Height (in.) of equilibrium value} \times \text{record speed (in./min.)}}{\text{Area (in.}^2\text{ of extrapolated curve)}}.$$

The cardiac output in litres per minute was then determined from this estimation multiplied by the total blood volume which was determined initially. Theoretical considerations of this method will be amplified in the discussion. As estimations were made at weekly intervals, potassium iodide was prescribed to be taken by the subjects for a few days before and after each test, in order to prevent uptake of the radioactive iodine by the thyroid.

From the recorded determinations the following estimations were made:

1. *Mean circulation time* (*MCT*) was measured objectively by a method which would include the transit time through the heart and lungs (32, 33). This parameter is determined on the curve for cardiac output by measuring the first moment (or the centre of gravity) of the extrapolated curve. By definition

$$MCT = \frac{\int_{T_1}^{\infty} ct\,dt}{\int_{T_1}^{\infty} c\,dt}$$

(Cyvin's formula) (34). In practice this is done by summing the products C_1T_1, C_2T_2, C_3T_3, C_nT_n and dividing this value by the sum of C_1, C_2, C_3 and C_n as described by Hamilton in 1932 (35). This method is cumbersome and does not significantly increase the accuracy of that time measurement from the moment of starting injection of Rihsa into the median basilic vein (x) until the peak activity is recorded over the precordium (y), that is, on Figure 3 the xy time interval is very nearly equal to the time interval from "a" to the projection of the centre of gravity of the exponentially extrapolated curve on the abscissa. Xy is very nearly equal to "ac" because the time concentration curve is skewed to the right (to the left on the recording). In six tracings checked at random, the mean difference between these two methods was less than 0.3 seconds. With mean circulation times observed in this study lying for the most part between 10 and 15 seconds, the error is relatively small compared to any subjective methods (< 3 per cent).

Another simple method for determining the mean circulation time in radiocardiographic work is employed by Shipley (36). The extrapolated curves are traced on index card paper, cutting out the enclosed area and finding the centre

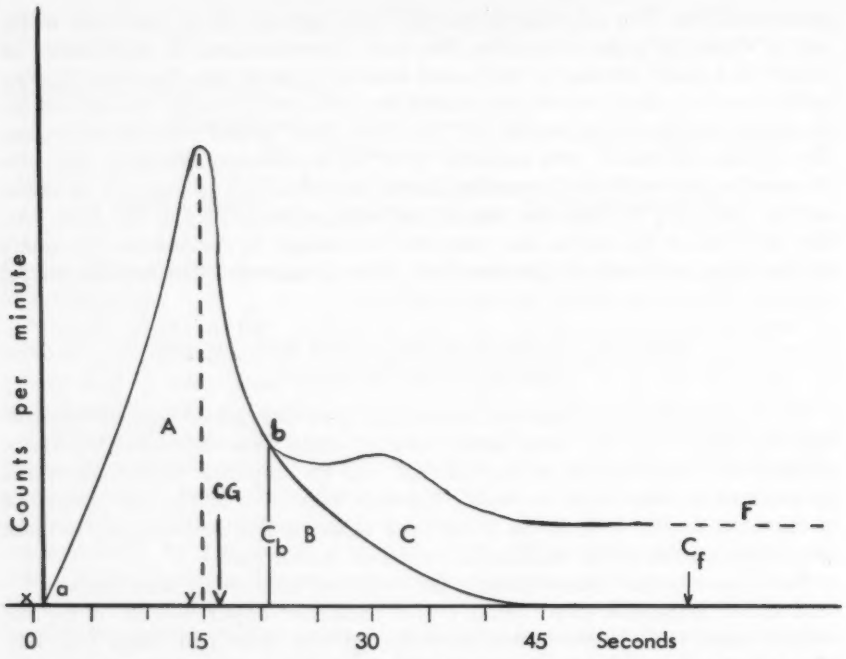


FIGURE 3. The *cardiac output* is derived from the area $(A + B)$ in square inches under the primary circulation tracing caused by the injected Rhisa, and extrapolated exponentially from point b to the base line in order to exclude the recirculation curve (bF). The final dilution of Rhisa is represented by the height Cf (inches). This height is multiplied by the paper speed (8 inches per minute), and the product divided by the area, which is measured by planimetry. The derived figure represents the cardiac output in blood volumes per minute. The latter figure is multiplied by the total blood volume, previously determined (see Fig. 4 or example). The *mean circulation time* is derived from the same tracing either by measuring the time xy in seconds (from moment of injection to moment of peak radioactivity), or the time interval from a to the projection of the centre of gravity of the primary extrapolated tracing on to the abscissa. The latter may be found empirically or mathematically (see text).

of gravity by balancing the cut-out on a knife edge. The errors by these two empirical methods (xy measure and balancing) are no greater than making multiple measurements on the curve and applying mathematics.

2. *Cardiac Index* $(CI) = \dfrac{\text{Cardiac output (litres/min.)}}{\text{Body surface area}}$.

3. (a) *Stroke Volume* $(SV) = \dfrac{\text{Cardiac output (litres/min.)}}{\text{Mean pulse rate/min.}}$.

(b) *Stroke Index* $(SI) = \dfrac{\text{Stroke volume}}{\text{Body surface area } (BSA)}$.

4. *Total peripheral resistance* (*TPR*) was estimated by the over-all resistance formula of Apiera (37) in which *TPR* in dynes/sec./cm.[5] equals

$$\frac{\text{Mean arterial B.P. (mmg.Hg)} \times 1332}{\text{Cardiac output in ml./sec.}}$$

or

$$\frac{\text{Mean arterial B.P. (mm.Hg)} \times 80}{\text{Cardiac output in litres}}.$$

Differences greater than 20 per cent in the above parameters were taken as significant (38).

5. *Cardiac power or left ventricular work* (*LVW*) was estimated as recommended by Remington and Hamilton (39) according to the formula:

$$LVW \text{ in kg. metres/min.} = \frac{13.5 \times \text{cardiac output (L/min.)} \times \text{mean arterial B.P. (mm.Hg).}}{1000}$$

This formula assumes that the specific gravity of blood is slightly greater than unity. Differences greater than 30 per cent are taken as significant.

6. The *intrathoracic blood volume index* (*ITBVI*) was derived from the formula:

$$\frac{\text{Mean circulation time} \times \text{cardiac output}}{60 \times BSA}.$$

A change greater than 15 per cent is considered to be significant (38, 40–44).

7. *Oxygen consumption* was measured on the respiration tracings recorded on a respirometer known as a Pulmotest.[1] This instrument was calibrated with oxygen so that a one centimetre rise in the slope indicated utilization of 300 ml. of oxygen. Paper speed on this recorder was 30 mm. per minute. This instrument is ordinarily employed as a recording bronchospirometer and was used in this study for oxygen consumption measurements by filling one bell with oxygen and allowing the oxygen to leak across to the other bell (filled with room air) via an electro-magnetic solenoid which is activated by the tidal volume. This instrument was connected to the patient via a short piece of corrugated tubing and a well-fitting face mask selected previously (as in Fig. 1). The same fitted mask was used for each subject during all the studies.

Results

The mean resting vital signs for each subject, together with the cardio-respiratory parameters derived from metabolic rate tables, the ventilation standards for use in artificial respiration described by Radford, and the cardiac output from the nomogram devised by Jackson, are summarized in Table I. The vital statistics, the blood volume and fractions and the mean control vital signs, together with the cardio-respiratory parameters obtained prior to administration of the intravenous anaesthetics, are summarized in Table II. The data obtained for each subject with each drug are tabulated in Tables III to IX.

[1]Made by J. H. Becker in Delft, Holland.

TABLE I

MEAN RESTING VITAL SIGNS AND PREDICTED CARDIO-RESPIRATORY PARAMETERS

	AB	LC	WH	NK	DS	EB	PB	AL	MEANS
Systolic Blood Pressure	112	121	110	125	106	119	110	111	114
Diastolic Blood Pressure	70	70	60	62	70	70	70	70	68
Pulse Pressure	42	51	50	63	36	49	40	41	46
Mean Blood Pressure	84	87	77	83	82	86	83	84	83
Pulse Rate	68	71	62	68	69	72	66	73	69
Respiration Rate	18	18	18	16	18	16	18	18	17.5
Tidal Volume**	380	420	400	500	370	560	350	390	420
Minute Volume**	6.84	7.85	7.20	8.00	6.65	8.98	6.30	6.82	7.30
Oxygen Consumption*	262	284	268	300	264	328	248	270	277
Circulation Time	15.5	14.6	11.8	10.6	11.9	16.7	14.2	11.2	13.3
Cardiac Output+	4.6	5.1	4.8	5.5	4.5	5.1	4.4	4.6	4.82
Index	2.55	2.52	2.60	2.62	2.42	2.22	2.63	2.35	2.48
Stroke Volume+	68	72	78	81	65	71	67	63	70
Index	38	35	42	39	35	31	40	32	36
Total Peripheral Resistance	1460	1370	1283	1203	1446	1346	1510	1462	1380
Left Ventricular Work	5.2	6.0	4.9	6.2	5.0	5.9	4.9	5.2	5.4
Intrathoracic Blood Volume	1.19	1.24	0.95	0.98	0.90	1.42	1.04	0.86	1.09

* Calculated from the Mayo Foundation Studies of 1936 modified to permit determination at "present age"
** Predicted from Nomogram of Radford
\+ Predicted from Nomogram of JAckson

Statistical analysis of these data is summarized in Tables X to XVI. The mean respiratory and haemodynamic effects of each intravenous anaesthetic are summarized in Tables XVII and XVIII respectively. Figures 4–8 show selected tracings which illustrate the typical effects observed.

The significant alteration with each drug is described below, first with regard to the acute effect, the changes from the resting and control values, and then the effects after the acute changes have passed (during "waking up" period).

Thiopental. Apnoea lasted approximately 30 seconds with the mean dose of 442 mg./M^2. Oxygen consumption and BMR decreased approximately 30 per cent in all subjects ($P < .01$). This effect persisted until the subject recovered. The change was accompanied by a 16 per cent rise in pulse rate, a 17 per cent fall in the mean blood pressure and a 23 per cent fall in the venous pressure. There was no significant alteration in the mean circulation time or cardiac output. Peripheral resistance and left ventricular work showed an inconsistent decrease. These changes indicated that a substantial quantity of the circulating blood volume was probably shifted to the capillary or venous side of the circulation.

During recovery, the depression of tidal volume was compensated for adequately by a rise in the respiration rate. The pulse rate compensated for the fall in blood pressure.

TABLE II

MEAN VALUES OF CARDIO-RESPIRATORY PARAMETERS—CONTROL STUDIES

Subject	Sex	Age	Build	Ht. cm.	Wt Kg.	BSA sq.m.	Respiration Rate /min.	Tidal Volume ml.	Minute Volume litres	Oxygen Consumption ml.	Metabolic Rate	Mean Pulse Rate /min	Mean Blood Pressure mm. Hg.	Mean Venous Pressure cm. H_2O	Plasma Volume litres & ml/kg	Red Cell Volume litres & ml/kg	Total Bd. Vol. litres & ml/kg	Body Haematocrit	Venous Haematocrit	BH/VH	Mean Circulation Time sec.	Cardiac Output and Index litres	Stroke Volume and Index litres	Total Peripheral Resistance dynes sec/cm^5	Left Ventricular Work kgM/min	Intrathoracic Blood Volume & Index litres
1 AB	M	22	Medium	175	68	1.80	16	560	9.0	316	+21	88	91	10.4	3.38 50	2.25 33	5.63 83	40.0	44.5	.90	15.5	6.1 3.4	70 39	1180	7.5	1.78 .99
2 LC	M	25	Medium	183	80	2.01	14	630	8.8	375	+33	93	91	11.2	3.56 44	2.62 33	6.18 77	42.4	47.1	.90	14.8	5.9 2.9	64 32	1230	7.2	1.92 .96
3 WH	M	23	Lean	175	74	1.85	16	510	8.1	313	+17	94	98	11.3	3.21 43	2.25 31	5.46 74	41.2	45.8	.90	11.8	6.3 3.4	67 36	1240	8.3	1.84 1.0
4 NK	M	23	Heavy	183	89	2.10	17	590	10.0	389	+30	110	92	11.9	3.66 41	2.58 29	6.24 70	41.4	46.0	.90	10.6	7.7 3.7	70 33	955	9.5	2.34 1.12
5 DS	M	23	Lean	183	66	1.86	18	570	10.2	325	+22	98	80	9.8	4.10 62	3.00 45	7.10 107	42.3	47.0	.90	11.9	7.0 3.7	72 39	915	7.5	2.70 1.45
6 EB	M	23	Heavy	191	102	2.31	11	810	8.9	341	+4	80	89	7.4	4.23 41	3.12 31	7.35 72	42.5	47.2	.90	16.7	5.3 2.2	66 29	1340	6.4	2.87 1.24
7 PB	M	22	Lean	175	60	1.67	13	620	8.0	365	+48	80	80	11.6	3.74 62	2.54 42	6.28 104	40.9	45.0	.91	14.2	5.3 3.2	66 39	1210	5.7	2.19 1.63
8 AL	M	31	Lean	188	72	1.96	12	820	9.8	377	+39	104	93	8.8	3.65 51	2.58 36	6.23 87	41.4	46.0	.90	11.2	5.7 2.9	55 28	1300	7.2	1.92 .98
Means		24		182	76	1.94	14	640	9.1	352	+31	93	90	10.3	3.70 49	2.61 34.9	6.18 84.2	41.4	46.0	.90	13.3	6.2 3.2	66.2 34.4	1171	7.4	2.20 1.17

TABLE III

PENTOTHAL: ACUTE EFFECTS

	Dose /M² mg.	O_2C ml.	BMR	PR_m /min	AP_m mm.Hg.	VP_m cm.H_2O	CT_m sec.	CO (P) litres	CO (R) litres	CI (P) litres	CI (R) litres	SI (P) ml.	SI (R) ml.	TPR (P) dynes-sec./cm^5	TPR (R) dynes-sec./cm^5	LVW (P) Kg.M/min	LVW (R) Kg.M/min	ITBVI (R) litres
1	c	280	+7	94	100	12.3-13.6	14.5	6.5	7.9	3.6	4.4	39	46	1230	1008	8.8	10.7	1.06
	472	200	-16	116	70	10.2	13.1	7.5	10.2	4.2	5.7	38	49	748	548	7.1	9.6	1.25
% Difference		-28.6	-23	23	-30	-22	-10	+15	29	17	30	-3	+7	-39	-46	-19	-10	+18
2	c	390	+38	100	88	10.2-12.3	12.2	7.5	9.9	3.8	4.9	37	49	940	712	8.9	11.8	1.00
	498	270	-4	116	72	8.2	8.8	7.6	9.9	3.8	4.9	34	41	757	582	7.4	9.6	.73
% Difference		-31	-42	16	-18	-27	-28	1	0	0	0	-8	-16	-20	-32	-17	-19	-27
3	c	300	+12	115	93	9.5-16.3	8.8	6.8	10.4	3.7	5.6	32	4.9	1092	715	8.5	13.1	1.11
	433	190	-29	125	70	5.4	12.6	8.5	9.8	4.6	5.3	37	42	658	572	8.0	9.2	1.11
% Difference		-37	-41	9	-25	-58	43	25	-6	24	-5	13	-14	-40	-20	-6	-30	0
4	c	380	+27	120	73	-PT	9.8	8.3	13.7	3.9	6.5	34	54	704	425	8.2	13.5	1.16
	333	260	-16	105	54	-PT	10.8	7.9	11.8	3.8	5.6	37	53	546	361	5.8	8.6	1.11
% Difference		-32	-43	-13	-26		10	-5	-14	-3	-14	9	-2	-22	-15	-29	-36	-5
5	c	315	+20	100	90	10.2-12.3	12.2	7.7	14.9	4.2	8.0	39	80	935	483	9.4	18.1	0.98
	323	240	-9	120	83	8.2	12.6	7.8	18.4	4.2	9.9	36	82	853	361	8.7	20.6	2.08
% Difference		-24	-29	20	-8	-27	3	1	24	0	24	-8	3	-9	-25	-7	14	112
6	c	315	-4	70	90	6.8	13.6	4.2	9.6	1.8	4.2	25	58	1715	750	5.1	11.6	0.94
	260*	240	-27	90	90	6.8	13.1	5.2	6.6	2.3	2.9	25	32	1384	1088	6.3	8.0	0.63
% Difference		-24	-23	29	0	0	-4	24	-31	28	-31	0	-46	-19	45	24	-31	-33
7	c	330	+34	77	83	10.2-11.0	15.9	5.1	13.2	3.1	7.9	40	61	1300	504	5.7	14.8	1.82
	598	250	+1	100	72	3.4	14.0	7.0	9.4	4.2	5.5	42	51	822	613	6.8	9.1	1.32
% Difference		-24	-33	30	-13	-7	-12	37	-29	36	-30	5	-16	-37	22	19	-39	-28

* Sleep dose +20%

PT = poor tracing

TABLE IV

SURITAL: ACUTE EFFECTS

	Dose /M² mg.	O_2C ml.	BMR	PR_m /min.	AP_m mm.Hg	VP_m cm.H_2O	CT_m sec.	CO (P) litres	CO (R) litres	CI (P) litres	CI (R) litres	SI (P) ml.	SI (R) ml.	TPR (P) dynes-sec	TPR (R) /cm⁵	LVW (P) Kg. M/min.	LVW (R) Kg. M/min.	LTBVI (R) litres
1	c	340	+30	88	87	- PT	15.5	6.2	5.6	3.4	3.1	40	35	1180	1240	7.3	6.6	0.81
	445	190	-27	100	77		12.2	7.9	6.8	4.3	3.8	44	38	780	928	8.2	7.2	0.77
% Difference		-44	-57	14	-12		-21	27	21	27	21	10	9	-34	-25	12	9	-5
2	c	360	+21	86	93	11-13.6	17.3	5.1	6.2	2.6	3.1	29	46	1455	1200	6.4	7.8	0.89
	398	280	-1	110	73	2.7	16.8	8.0	6.8	3.9	3.4	36	31	730	856	7.9	6.7	0.95
% Difference		-22	-29	28	-22	-78	-3	57	7	57	9	24	33	-50	-29	23	-14	7
3	c	340	+27	85	103	13.6-20	13.1	6.4	7.1	3.5	3.8	41	45	1286	1160	8.9	9.9	0.84
	486	260	-3	90	80	11.6	16.4	7.5	6.6	4.1	3.6	45	39	854	968	8.1	7.1	0.98
% Difference		-24	-30	6	-22	-31	25	17	-7	17	-5	10	-13	-37	-17	-9	-28	17
4	c	370	+24	105	83	- PT	10.8	7.2	10.0	3.4	4.8	32	45	924	664	8.1	11.2	0.86
	381	300	0	120	73		10.8	8.7	10.6	4.1	5.1	35	42	672	545	8.6	10.4	0.91
% Difference		-23	-24	14	-12		0	21	6	21	6	9	-7	-27	-18	6	-7	6
5	c	330	+25	100	77	8.2-13.6	10.3	7.9	12.8	4.3	6.9	42	69	778	480	8.2	13.3	1.18
	323	300	+14	110	80	5.5	10.3	6.8	17.0	3.7	9.1	33	83	940	376	7.3	18.3	1.57
% Difference		-9	-11	10	4	-50	0	-14	33	-14	32	-21	20	21	-22	-11	38	33
6	c	310	-5	90	73	8.2	22	6.5	8.8	2.8	3.8	32	42	900	664	6.4	8.7	1.39
	217*	250	-24	105	77	5.5	15.4	7.1	6.6	3.1	2.9	29	27	867	928	7.4	6.9	0.74
% Difference		-19	-19	17	6	-33	-30	9	-25	9	-24	-9	-36	-4	40	16	-21	-47
7	c	400	+62	88	82	11-19	PT	5.7		3.4		39		1150		6.3		
	415	315	+28	96	70	12.3		6.4		3.8		40		874		6.0		
% Difference		-21	-34	9	-10	-18		12		12		3		-24		-5		

* Sleep dose +20%

PT = poor tracing

TABLE V

EVIPAL: ACUTE EFFECTS

	Dose /M² mg.	O_2C ml.	BMR	PR_m /min.	AP_m mm.Hg	VP_m cm.H_2O	CT_m sec.	CO (P) litres	CO(R) litres	CI (P) litres	CI (R) litres	SI (P) ml.	SI (R) ml.	TPR (P) dynes-sec	TPR (R) /cm⁵	LVW (P) Kg.M/min.	LVW (R)	TBVI (R) litres
1	c	315	+20	90	90	9.5-11	14.5	6.7	6.8	3.7	3.8	42	42	1123	1056	8.1	8.3	0.92
	556	310	+18	120	87	5.5	13.6	8.5	9.0	4.7	5.0	40	60	820	800	10.0	10.6	1.16
% Difference		-2	-2	33	-3	-53	-6	27	32	27	31.6	-5	43	-27	-24	24	28	26
2	c	330	+17	95	97	11	13.1	6.1	6.8	3.0	3.4	32	42	1207	1140	8.0	8.9	0.74
	472	325	+15	115	77	12.9	10.8	8.7	5.7	4.3	2.8	38	28	700	1080	9.0	5.9	0.52
% Difference		-2	-2	21	21	17	-18	43	-16	43	-18	19	-33	-42	-5	13	-34	-30
3	c	325	+21	80	97	6.8-7.5	11.2	5.2	7.1	2.8	3.8	35	48	1490	1088	6.8	9.8	0.72
	514	280	+5	100	83	6.8	13.6	6.6	13.6	3.6	7.3	36	74	1005	488	7.4	15.4	1.66
% Difference		-14	-6	25	14	-5	21	27	92	29	92	3	54	-33	-55	9	57,	131
4	c	320	+7	120	107	PT	9.8	9.4	15.4	4.5	7.4	38	62	911	549	13.6	22.3	1.21
	417	400	+33	130	83		8.4	8.2	14.3	3.9	6.8	31	52	819	464	9.2	16.0	0.96
% Difference		25	+26	8	22		-14	-13	-8	-13	-8	-18	-16	-10	-16	-32	-28	-21
5	c	330	+25	100	83	11-13.6	14.5	8.7	13.4	4.7	7.2	47	72	764	488	9.7	15.0	1.74
	538	290	+10	125	77	8.2	15.9	9.2	17.0	5.0	9.2	41	73	669	362	9.5	17.6	2.42
% Difference		-12	-15	25	-7	-33	10	6	27	6	28	-13	1	-12	-26	-2	17	39
6	c	360	+10	72	90	6.8-9.6	23.8	4.0	9.5	1.7	4.2	24	58	1795	758	4.9	11.5	1.63
	260*	290	-11	105	83	6.8	19.7	5.9	8.8	2.6	3.8	24	38	1125	754	6.6	9.9	1.25
% Difference		-19	-21	46	-8	-17	-17	48	-7	53	-10	0	-35	-37	1	35	-14	-23
7	c	350	+42	80	77	17-30	PT	5.3		3.2		39		616		5.5		
	598	300	+22	110	70	16.3		7.0		4.2		40		800		6.6		
% Difference		-14	-20	38	9	-31		32		31		3		30		20		

* Sleep dose +20%

PT = poor tracing

TABLE VI

TRANSITHAL: ACUTE EFFECTS

	Dose /M² mg.	O_2C ml.	BMR	PR_m /min.	AP_m mm.Hg	VP_m cm.H_2O	CT_m sec.	CO (P) litres	CO (R) litres	CI (P) litres	CI (R) litres	SI (P) ml.	SI (R) ml.	TPR (P) dynes-sec	TPR (R) /cm⁵	LVW (P) Kg.	LVW (R) M/min.	LTBVI (R) litres
1	c	300	+15	94	87	16.3-19	16.4	6.6	5.6	3.7	3.1	39	33	1053	1240	7.8	6.6	0.85
	556	300	+15	106	73	10.2	14.0	7.6	7.9	4.2	4.4	40	41	759	757	7.5	7.8	1.02
	% Difference	0	0	9	-16	-42	-15	15	41	14	42	3	24	-28	-39	-4	18	20
2	c	420	+48	100	80	8.2	13.1	8.0	9.9	4.0	4.9	40	49	800	648	8.6	10.7	1.07
	898	390	+38	104	63	8.2	12.2	8.0	9.3	4.0	4.6	38	44	628	542	6.8	7.9	0.94
	% Difference	-1	-10	4	-21	0	-7	0	-6	0	-6	-5	-10	-22	-16	-21	-26	-12
3	c	290	+9	90	83	13.6-19	9.8	7.2	11.4	3.9	6.2	43	68	923	582	8.1	12.8	1.00
	540	190	-29	110	90	12.2	8.4	8.3	7.6	4.5	4.1	41	37	867	944	10.1	9.3	0.58
	% Difference	-35	-38	22	8	-25	-14	15	-33	15	-34	-5	-46	-6	62	25	-27	-42
4	c	420	+40	120	107	PT	11.7	9.4	11.8	4.8	5.6	38	47	912	734	7.5	17.1	1.10
	476	300	0	110	83		11.7	7.3	11.8	3.5	5.6	31	51	910	562	8.2	13.2	1.10
	% Difference	-29	-40	-8	-22		0	-22	0	-27	0	-18	9	0	-23	9	-23	0
5	c	320	+22	95	70	11	11.2	6.3	14.9	3.4	8.0	36	85	888	336	6.0	14.1	1.50
	753	310	+18	110	57	11	PT	8.5		4.6		42		535		6.5		
	% Difference	-3	-4	16	-19	0		35		35		17		-40		8		
6	c	365	+12	90	93	8.2	14.0	5.0	11.8	2.2	5.1	24	57	1484	631	6	14.8	1.19
	433*	270	-17	100	87	5.5	13.6	7.1	7.4	3.1	3.2	31	32	980	836	8	8.7	0.73
	% Difference	-26	-29	11	-7	-33	-3	42	-37	41	-37	54	-44	-34	33	32	-41	-39
8	c	380	+41	106	93	10-12.3	10.3	5.9	10.6	3.0	5.4	28	52	1260	700	7.4	13.3	0.93
	920	270	0	124	67	8.2	10.8	7.0	7.5	3.6	3.8	29	31	806	7.4	6.3	6.8	0.69
	% Difference	-29	-41	17	-28	-3	5	19	-29	20	-30	4	-40	-36	2	-15	-49	-26

* Sleep dose +20%

PT= poor tracing

TABLE VII

Neraval: Acute Effects

	Dose /M² mg.	O_2C ml.	BMR	PR_m /min.	AP_m mm.Hg	VP_m cm.H_2O	CT_m sec.	CO (P) litres	CO (R) litres	CI (P) litres	CI (R) litres	SI (P) ml.	SI (R) ml.	TPR (P) dynes-sec /cm^5	TPR (R)	LVW (P) Kg.	LVW (R) M/min.	ITBVI (R) litres
1	c	320	+22	88	93	8.2-11	14.5	5.3	8.5	3.0	4.8	33	53	1400	872	6.7	10.7	1.14
	264*	280	+7	88	87	5.5	PT	6.1		3.4		39		1140		7.2		
	% Difference	-13	-15	0	-7	-43		15		-13		18		-19		8		
2	c	390	+38	88	83	13.6	19.2	5.7	7.4	2.8	3.7	33	42	1222	898	6.4	8.3	1.18
	398	310	+ 8	100	60	11	14.5	7.3	7.4	3.6	3.7	36	37	658	648	5.9	6.0	0.89
	% Difference	-21	-30	14	-28	-19	-25	28	0	29	0	9	-12	-46	-28	-8	-28	-25
3	c	305	+14	118	100	17-20	13.6	8.2	9.3	4.4	5.0	38	43	978	856	11.1	12.5	1.14
	378	240	-10	104	90	13.6	16.4	7.9	13.1	4.3	7.1	41	68	912	548	9.6	15.9	1.93
	% Difference	-21	-24	-12	-10	-27	21	-4	41	-2	42	8	58	-7	-36	-14	27	69
4	c	420	+40	100	93	10.2-13.6	11.2	6.0	14.6	2.9	6.9	29	70	1240	510	7.5	18.3	1.30
	405	310	+4	110	73	6.8	10.8	7.8	6.2	3.7	3.0	34	27	740	944	7.7	6.1	0.53
	% Difference	-26	-36	10	-22	-57	-4	30	-58	28	-57	17	-61	-40	85	3	-67	-59
5	c	330	+25	110	78	10	10.3	8.9	PT	4.8		44		702		7.7		
	376	320	+22	95	64	6.8	10.8	6.7		3.6		38		766		5.8		
	% Difference	-3	-3	-14	-18	-32	5	-25		-25		-14		9		-25		
6	c	300	-8	75	97	6.8	14.5	4.9	9.6	2.2	4.2	28	56	1582	808	6.4	12.6	1.00
	433	250	-24	104	83	9.6	11.2	6.9	10.1	3.0	4.4	29	42	963	656	7.7	11.3	0.82
	% Difference	-17	-16	39	-14	-41	-23	41	5	36	5	4	-25	-39	-19	20	-10	-18
8	c	360	+34	110	93	9.6	12.2	6.1	11.8	3.1	6.0	28	47	1220	630	7.7	14.8	1.22
	510	220	-18	95	70	4.1	11.2	5.9	9.4	3.0	4.8	32	50	950	596	5.6	8.9	0.90
	% Difference	-39	-52	-14	-25	-57	-8	-3	-20	-3	-20	14	6	-22	-5	-27	-40	-26

* Sleep dose

PT = poor tracing

TABLE VIII

Compound 25398: Acute Effects

	Dose /M2 mg.	O_2C ml.	BMR	PR_m /min.	AP_m mm.Hg	VP_m cm.H_2O	CT_m sec.	CO (P) litres	CO (R) litres	CI (P) litres	CI (R) litres	SI (P) ml.	SI (R) ml.	TPR (P) dynes-sec	TPR (R) /cm^5	LVW (P) Kg.M/min.	LVW (R) Kg.M/min.	ITBVI (R) litres
1	c	340	+30	90	83	6.8-9.5	16.8	7.7	8.5	4.3	4.7	48	52	888	782	8.6	9.5	1.32
	278	270	+3	120	67	3.4	13.6	9.6	7.3	5.3	4.1	46	34	559	726	8.7	6.6	0.92
% Difference		-21	-27	33	-19	-58	-19	25	-14	23	-13	-4	-35	-37	-7	1	-31	-30
2	c	375	+34	100	100	11-13.6	12.6	6.8	9.9	3.4	5.0	34	49	1175	808	9.2	13.4	1.04
	224	230	-18	135	93	9.5	11.7	7.9	6.8	4.0	3.4	30	38	944	1096	9.9	8.5	0.66
% Difference		-39	-52	35	-7	-25	-7	16	-31	18	-32	-12	-22	-20	36	8	-37	-37
3	c	315	+18	90	100	11-16.3	14	6.3	9.0	3.4	4.9	38	54	1268	888	8.5	12.1	1.14
	270	275	+3	130	83	8.2	10.8	8.4	10.4	4.5	5.6	36	43	790	638	9.9	11.7	1.01
% Difference		-13	-15	44	-17	-40	-23	33	16	32	14	-5	-20	-38	-28	17	-3	-11
4	c	390	+30	116	83	13.6-15	9.8	7.5	15.0	3.7	7.2	31	62	885	442	8.4	16.8	1.17
	238	370	+24	132	83	10.2	14.5	8.5	8.1	4.1	3.9	31	29	781	818	9.5	9.1	0.93
% Difference		-5	-6	14	0	-29	48	13	-46	11	-46	0	-53	-12	85	13	-46	-21
5	c	300	+14	100	73	PT	10.3	7.2	14.9	3.9	8.0	39	80	812	432	7.1	14.7	1.37
	242	260	-1	150	77		10.8	8.4	9.9	4.5	5.3	30	35	735	624	8.7	10.3	0.96
% Difference		-13	-15	50	6		5	17	-34	15	-34	-23	-56	-10	44	23	-30	-30
6	c	370	+13	84	80	PT	14.5	6.8	11.7	2.9	5.1	35	60	941	546	7.3	12.6	1.22
	217*	350	+7	100	77		14.0	7.7	8.8	3.3	3.8	33	38	802	700	8.0	9.2	0.89
% Difference		-5	-6	19	-4		-3	13	-25	14	-26	-6	-37	-15	28	10	-27	-27
7	c	380	+54	76	77	8.2	12.6	5.1	6.3	3.1	3.8	40	50	1208	976	5.3	6.6	0.79
	300	250	+1	120	60	2.7	13.6	8.7	8.2	5.2	4.8	44	41	552	586	7.0	6.6	1.11
% Difference		-34	-53	58	-22	-67	8	71	30	68	26	10	-18	-54	-40	32	0	41

* Sleep dose + 20%

PT = poor tracing

TABLE IX

DOLITRONE: ACUTE EFFECTS

	Dose /M² mg.	O_2C ml.	BMR	PR_m /min.	AP_m mm.Hg	VP_m cm.H_2O	CT_m sec.	CO (P) litres	CO (R) litres	CI (P) litres	CI (R) litres	SI (P) ml.	SI (R) ml.	TPR (P) dynes-sec	TPR (R) /cm⁵	LVW (P) Kg.M/min	LVW (R)	ITBVI (R) litres
1	c	315	+20	75	90	9.5-11	16.4	4.1	5.6	2.3	3.1	31	42	1760	1288	5.0	6.8	0.85
	445	300	+15	110	87	8.2	15.0	5.5	5.1	3.2	2.8	28	26	1265	1570	6.4	4.5	0.71
% Difference		-5	-5	47	-3	-20	-9	34	-9	39	-10	-10	-38	-28	22	28	-34	-17
2	c	360	+28	85	90	13.6	15.0	4.6	6.2	2.3	3.1	27	36	1562	1160	5.6	7.9	0.77
	498	300	+6	110	67	11	10.3	6.5	6.2	3.2	3.1	30	28	825	864	5.1	5.6	0.53
		-17	-22	29	-26	-19	-31	41	0	39	0	11	-22	-47	-26	-9	-29	-31
3	c	315	+18	94	93	8.9-10.2	12.2	7.3	9.3	3.9	5.0	44	48	1012	800	9.2	11.7	1.02
	541	290	+9	130	90	6.8	9.8	9.3	7.1	5.0	3.8	41	30	775	1012	11.3	8.6	0.63
% Difference		-8	-9	38	-3	-29	-20	27	-24	28	-24	-7	-38	-23	27	23	-27	-38
4	c	420	+40	100	97	PT	11.2	6.5	12.4	3.1	5.9	31	59	1192	624	8.5	16.2	1.10
	357	350	+18	130	97		12.2	8.4	10.6	4.0	5.1	31	39	925	732	11.3	13.5	1.03
% Difference		-17	-22	30	0		9	29	-15	29	-14	0	-34	-22	17	33	-17	-6
5	c	320	+22	85	93	8.2-10.2	14.5	5.2	14.9	2.8	8.0	32	95	1248	500	6.4	18.7	1.93
	538	260	-1	120	70	11	14.0	8.0	9.9	4.3	5.3	36	44	788	566	7.6	9.4	1.24
% Difference		-19	-23	41	-25	20	-3	54	-34	54	-34	13	-54	-37	13	19	-50	-36
6	c	370	+13	75	97	PT	14.5	5.2	12.4	2.3	5.4	28	72	1490	624	6.8	16.2	1.30
	380*	330	+1	105	93		12.2	6.3	5.2	2.7	2.3	26	22	1210	656	7.9	6.5	0.46
% Difference		-11	-12	40	-4		-16	21	-58	17	-57	-7	-69	-19	5	16	-60	-65
7	c	390	+44	100	93	6.8-8.9	9.8	6.0	9.4	3.1	4.8	31	48	1270	792	7.5	11.8	0.78
	510	260	-3	128	70	3.4	8.8	8.5	8.7	4.3	4.4	34	35	658	644	8.0	8.2	0.62
% Difference		-33	-47	28	-25	-57	-10	42	-7	39	-8	10	-27	-48	-19	7	-31	-21
8	c	300	+9	83	100	11	PT	6.0		3.1		37		1332		8.1		-
	520	215	-22	135	80	8.2	9.4	11.0	10.0	5.7	5.2	43	38	582	640	11.9	10.8	0.82
% Difference		-28	-31	63	-20	-26	-	83	-	84	-	16.0	-	56	-	47	-	-

* Sleep dose + 20% PT = poor tracing

TABLE X

PENTOTHAL: STATISTICAL ANALYSIS OF ACUTE EFFECTS

PARAMETERS	Percent Difference	Standard Deviation	Standard Error	Fisher t Value	Probability
Metabolic Rate	-33	8.8	3.3	-10	.01
Mean Pulse Rate	+16	14.6	5.6	+2.9	.05
Mean Arterial Pressure	-17	10.8	4.1	-4.3	.01
Mean Venous Pressure	-23	20.3	8.3	-2.8	.05
Mean Circulation Time	+.5	22.4	8.5	+.06	ns
Cardiac Output (Predicted)	+14	15.8	6.0	+2.4	ns
Cardiac Output (Recorded)	-4	23.3	8.9	-.4	ns
Cardiac Index (Predicted)	+14	15.5	5.9	+2.5	.05
Cardiac Index (Recorded)	-4	23.9	9.0	-.4	ns
Stroke Index (Predicted)	+1	8.0	3.0	+.4	ns
Stroke Index (Recorded)	-12	17.5	6.6	-1.8	ns
Total Peripheral Resistance (Predicted)	-26	12.1	4.6	-5.8	.01
Total Peripheral Resistance (Recorded)	-10	32.4	12.2	-.8	ns
Left Ventricular Work (Predicted)	-5	19.8	7.5	-.7	ns
Left Ventricular Work (Recorded)	-21	18.5	7.0	-3.1	.05
Intrathoracic Blood Volume Index (Recorded)	+5	50.9	19.2	+.3	ns

ns = not significant

TABLE XI

SURITAL: STATISTICAL ANALYSIS OF ACUTE EFFECTS

PARAMETERS	Percent Difference	Standard Deviation	Standard Error	Fisher t Value	Probability
Metabolic Rate	-29	14.6	5.5	-5.3	.01
Mean Pulse Rate	+14	7.2	2.7	+5.1	.01
Mean Arterial Pressure	-7	13.1	5.0	-1.4	ns
Mean Venous Pressure	-42	23.1	10.3	-4.1	.05
Mean Circulation Time	-5	19.3	7.9	-.6	ns
Cardiac Output (Predicted)	+19	+21.3	8.1	+2.3	ns
Cardiac Output (Recorded)	+6	20.4	8.3	+.7	ns
Cardiac Index (Predicted)	+19	20.6	7.8	+2.4	.05
Cardiac Index (Recorded)	+6	19.8	8.1	+.9	ns
Stroke Index (Predicted)	+4	14.9	5.6	+.6	ns
Stroke Index (Recorded)	-10	22.2	9.1	-1.1	ns
Total Peripheral Resistance (Predicted)	-22	23.3	8.8	-2.5	.05
Total Peripheral Resistance (Recorded)	-12	25.6	10.5	-1.1	ns
Left Ventricular Work (Predicted)	+5	13.3	5.0	+.9	ns
Left Ventricular Work (Recorded)	-4	24.0	9.8	-.4	ns
Intrathoracic Blood Volume Index (Recorded)	+2	27.0	11.0	+.2	ns

ns = not significant

TABLE XII

EVIPAL: STATISTICAL ANALYSIS OF ACUTE EFFECTS

PARAMETERS	Percent Difference	Standard Deviation	Standard Error	Fisher t Value	Probability
Metabolic Rate	-6	16.1	6.1	-.9	ns
Mean Pulse Rate	+28	12.2	4.6	+6.1	.01
Mean Arterial Pressure	-12	7.2	2.7	-4.5	.01
Mean Venous Pressure	-17	27.2	11.1	-1.6	ns
Mean Circulation Time	-4	16.1	6.6	-.6	ns
Cardiac Output (Predicted)	+24	21.1	7.8	+3.1	.05
Cardiac Output (Recorded)	+20	36.9	15.1	+1.3	ns
Cardiac Index (Predicted)	+24	22.3	8.4	+3.0	.05
Cardiac Index (Recorded)	+20	41.1	16.8	+1.2	ns
Stroke Index (Predicted)	-2	12.1	4.6	-.4	ns
Stroke Index(Recorded)	+2	38.2	15.6	+2.0	ns
Total Peripheral Resistance (Predicted)	-19	24.6	9.3	-2.0	ns
Total Peripheral Resistance (Recorded)	-21	19.7	8.0	-2.6	.05
Left Ventricular Work (Predicted)	+9	21.8	8.2	+1.1	ns
Left Ventricular Work (Recorded)	+4	35.6	14.5	+.3	ns
Intrathoracic Blood Volume Index (Recorded)	+20	61.0	24.9	+.8	ns

ns = not significant

TABLE XIII

TRANSITHAL: STATISTICAL ANALYSIS OF ACUTE EFFECTS

PARAMETERS	Percent Difference	Standard Deviation	Standard Error	Fisher t Value	Probability
Metabolic Rate	-23	17.1	6.7	-3.4	.05
Mean Pulse Rate	+10	10.0	3.8	+2.6	.05
Mean Arterial Pressure	-15	12.2	4.6	-3.2	.05
Mean Venous Pressure	-17	18.1	7.6	-2.3	ns
Mean Circulation Time	-6	7.8	3.2	-1.8	ns
Cardiac Output (Predicted)	+15	21.4	8.1	+1.8	ns
Cardiac Output (Recorded)	-11	29.6	12.1	-.9	ns
Cardiac Index (Predicted)	+15	22.7	8.6	+1.6	ns
Cardiac Index (Recorded)	-11	30.0	12.2	-.9	ns
Stroke Index (Predicted)	+6	23.8	9.0	+.6	ns
Stroke Index (Recorded)	-18	29.9	12.2	-1.5	ns
Total Peripheral Resistance (Predicted)	-14	15.3	5.8	-4.1	.01
Total Peripheral Resistance (Recorded)	+3	38.0	15.5	+.2	ns
Left Ventricular Work (Predicted)	+5	19.5	7.4	+.7	ns
Left Ventricular Work (Recorded)	-25	23.3	9.5	-2.6	.05
Intrathoracic Blood Volume Index (Recorded)	-17	23.9	9.8	-1.7	ns

ns = not significant

TABLE XIV

NERAVAL: STATISTICAL ANALYSIS OF ACUTE EFFECTS

PARAMETERS	Percent Difference	Standard Deviation	Standard Error	Fisher t Value	Probability
Metabolic Rate	-25	16.2	6.1	-4.1	.01
Mean Pulse Rate	+3	19.2	7.3	+.5	ns
Mean Arterial Pressure	-17	7.7	2.9	-6.0	.01
Mean Venous Pressure	-39	14.6	5.5	-7.2	.01
Mean Circulation Time	-6	17.1	7.0	0.8	ns
Cardiac Output (Predicted)	+12	23.3	8.8	+1.3	ns
Cardiac Output (Recorded)	-6	36.6	16.2	-.4	ns
Cardiac Index (Predicted)	+11	20.0	8.3	+1.3	ns
Cardiac Index (Recorded)	-6	36.1	16.1	-.4	ns
Stroke Index (Predicted)	+8	10.9	4.1	+2.0	ns
Stroke Index (Recorded)	-7	43.9	19.6	-.3	ns
Total Peripheral Resistance (Predicted)	-23	20.0	7.6	-3.1	.05
Total Peripheral Resistance (Recorded)	-.6	49.2	22.0	-.03	ns
Left Ventricular Work (Predicted)	-6	17.4	6.6	0.9	ns
Left Ventricular Work (Recorded)	-23	35.0	15.7	-1.5	ns
Intrathoracic Blood Volume (Index (Recorded)	-12	48.1	21.5	-.5	ns

ns = not significant

TABLE XV

COMPOUND 25398: STATISTICAL ANALYSIS OF ACUTE EFFECTS

PARAMETERS	Percent Difference	Standard Deviation	Standard Error	Fisher t Value	Probability
Metabolic Rate	-25	20.1	7.6	+3.3	.05
Mean Pulse Rate	+36	16.0	6.0	+6.0	.01
Mean Arterial Pressure	-9	10.5	4.0	-2.3	ns
Mean Venous Pressure	-43	19.0	8.0	-5.1	.01
Mean Circulation Time	+1	23.5	8.9	+.1	ns
Cardiac Output (Predicted)	+27	20.6	7.8	+3.4	.05
Cardiac Output (Recorded)	-15	27.8	10.5	-1.4	ns
Cardiac Index (Predicted)	+26	22.0	8.3	+3.1	.05
Cardiac Index (Recorded)	-16	31.3	11.8	-1.3	ns
Stroke Index (Predicted)	-6	10.2	3.9	-1.5	ns
Stroke Index (Recorded)	-34	15.6	5.9	-5.8	.01
Total Peripheral Resistance (Predicted)	-26	16.9	6.4	-4.1	.01
Total Peripheral Resistance (Recorded)	+17	44.2	16.7	+1.0	ns
Left Ventricular Work (Predicted)	+15	10.2	3.9	+3.8	.01
Left Ventricular Work (Recorded)	-25	17.0	6.4	-3.9	.01
Intrathoracic Blood Volume Index (Recorded)	-16	26.4	10.0	-1.6	ns

ns = not significant

TABLE XVI

DOLITRONE: STATISTICAL ANALYSIS OF ACUTE EFFECTS

PARAMETERS	Percent Difference	Standard Deviation	Standard Error	Fisher t Value	Probability
Metabolic Rate	-21	13.4	4.7	-4.6	.01
Mean Pulse Rate	+39	11.5	4.1	+9.6	.01
Mean Arterial Pressure	-13	11.5	4.1	-3.2	.05
Mean Venous Pressure	-22	24.5	10.0	-2.2	NS
Mean Circulation Time	-11	12.7	4.8	-2.4	NS
Cardiac Output (Predicted)	+41	19.7	7.0	+5.9	.01
Cardiac Output (Recorded)	-21	19.8	7.5	-2.8	.05
Cardiac Index (Predicted)	+41	20.3	7.2	+5.7	.01
Cardiac Index (Recorded)	-21	19.5	7.4	-2.8	.05
Stroke Index (Predicted)	+ 3	10.3	3.6	+ .9	NS
Stroke Index (Recorded)	-40	16.2	6.1	-6.6	.01
Total Peripheral Resistance (Predicted)	-35	14.0	4.9	-7.2	.01
Total Peripheral Resistance (Recorded)	+ 4	20.5	7.7	+ .5	NS
Left Ventricular Work (Predicted)	+20	16.9	6.0	+3.4	.05
Left Ventricular Work (Recorded)	-35	14.7	5.6	-6.3	.01
Intrathoracic Blood Volume Index (Recorded)	-30	19.0	7.1	-4.3	.01

ns = not significant

Thiamylal. The alterations in respiratory and haemodynamic parameters observed with this drug were similar to those for thiopental. The differences observed may be explained by the somewhat smaller doses of thiamylal administered, and may substantiate early clinical impressions of slightly greater potency of thiamylal with cardio-respiratory effects similar to those of thiopental.

In comparing the predicted changes with the recorded experimental data for both thiopental and thiamylal there is a depressed response by the heart, a lesser fall in total peripheral resistance and a greater fall in left ventricular work. These are indicative of cardiac depression by both thiopental and thiamylal at the dose level employed. However, the depression was not reflected in any significant fall in cardiac output.

Hexobarbital. The mean period of apnoea with this drug was 7 seconds with the mean dose of 517 mg./M^2. There was virtually no depression of the respiration or the metabolic rate. The pulse rate rose 28 per cent while the mean arterial pressure fell 12 per cent. The mean venous pressure tended to fall, but this was not consistent. Cardiodynamic parameters changed in the

TABLE XVII

SUMMARY OF MEAN CHANGES IN RESPIRATION WITH INTRAVENOUS ANAESTHETICS

	Time	2x Sleep dose.mg/M^2		BMR	R.R.	% Diff	T.V.	% Diff	M.V.	% Diff
PENTOTHAL (7 subjects)	R				17.5		420		7.3	
	C			+19	14	-20	640	+52	9.0	+23
	A	442	32"							
	T			-33	24	+37	360	-14	8.6	+18
SURITAL (7 subjects)	R				17.5		420		7.3	
	C			+27	14	-20	620	+48	8.7	+19
	A	402	23"							
	T			-29	20	+14	330	-21	6.6	-10
EVIPAL (7 subjects)	R				17.5		420		7.3	
	C			+21	14	-20	610	+45	8.6	+18
	A	517	7"							
	T			-6	21	+20	420	0	8.8	+21
TRANSITHAL (7 subjects)	R				17.5		420		7.3	
	C			+28	15	-14	620	+48	9.3	+27
	A	637	12"							
	T			-23	20	+14	360	-14	7.2	-1
NERAVAL (7 subjects)	R				17.5		420		7.3	
	C			+24	15	-14	640	+52	9.6	+31
	A	432	6"							
	T			-25	18	+3	330	-21	6.0	-18
LILLY 25398 (7 subjects)	R				17.5		420		7.3	
	C			+28	16	-9	570	+36	9.6	+31
	A	273	82"							
	T			-25	18	+3	300	-29	6.9	-5
DOLITRONE (8 subjects)	R				17.5		420		7.3	
	C			+24	14	-20	660	+57	9.1	+25
	A	512	8"							
	T			-21	22	+26	390	-7	8.6	+18

R = Resting C = Control Study A = Period of Apnoea in seconds
T = Mean during 10 - 15 minutes after acute changes have stabilized
BMR = Basal metabolic rate RR = Respiration Rate
TV = Tidal Volume MV = Minute Volume

direction predicted showing a tendency to increased cardiac output and decreased total peripheral resistance without significant alteration in the left ventricular work. On the whole, hexobarbital had far less effect on either respiration or haemodynamics than thiopental and thiamylal for the corresponding anaesthetic state.

Buthalitone. The mean period of apnoea was 12 seconds with the mean dose of 637 mg./M^2. This was followed by a slight depression of respiration during the period of action of this drug. There was a significant fall in the metabolic rate (23 per cent). The pulse rate rose 10 per cent while the mean arterial pressure fell 15 per cent. This was accompanied by an inconsistent fall in mean venous pressure. Cardiodynamic alterations were inconsistent but tended towards a slight fall in cardiac output without any significant change in the total peripheral resistance. However, the left ventricular work decreased by 25 per cent. In the parameters studied, this drug has an effect which is not unlike that of hexobarbital, except for the greater apparent effect on the heart.

Methitural. Although the potency of this drug is similar to that of thiopental and one-third greater than that of buthalitone, according to the dose adminis-

TABLE XVIII

SUMMARY OF MEAN HAEMODYNAMIC EFFECTS WITH INTRAVENOUS ANAESTHETICS

DRUG		SBP	% Diff.	DBP	% Diff.	BP_m	% Diff.	PP_m	% Diff.	PR_m	% Diff.
PENTOTHAL	R	114		68		83		46		69	
(7 subjects)	C	119	+ 4.4	72	+ 5.9	82	- 1.2	47	+ 2.2	85	±23
	A	97	-15	62	- 8.8	74	-10.8	35	-24	111	+61
	T	98	-14	60	-17.7	73	-12	40	-13	96	+39
SURITAL	R	114		68		83		46		69	
(7 subjects)	C	121	+ 6.1	72	+ 5.9	88	+ 6	49	+ 6.5	93	+35
	A	103	- 9.7	62	- 8.8	76	- 8.4	41	-11	104	+51
	T	103	- 9.7	63	- 7.4	76	- 8.4	40	-13	103	+49
EVIPAL	R	114		68		83		46		69	
(7 subjects)	C	137	+20.2	75	+10.3	96	+15.7	62	+35	95	+37
	A	107	- 6.1	66	- 3	80	- 3.6	41	-11	115	+66
	T	115	+ 1	63	- 7.4	80	- 3.6	52	+13	116	+68
TRANSITHAL	R	114		68		83		46		69	
(7 subjects)	C	126	+10.5	68	0	87	+ 4.8	58	+26	100	+45
	A	102	- 9.7	61	-10.3	75	- 9.7	42	- 8.7	109	+58
	T	105	- 8.6	61	-10.3	76	- 8.4	44	- 4.3	109	+58
NERAVAL	R	114		68		83		46		69	
(7 subjects)	C	119	+ 4.4	75	+10.3	90	+ 8.4	44	- 4.3	88	+28
	A	102	-10.5	61	-10.3	75	- 9.7	41	-11	100	+45
	T	103	-10	62	-10.3	75	- 9.7	41	-11	87	+26
Lilly 25398	R	114		68		83		46		69	
(7 subjects)	C	124	+ 8.8	70	+ 3	88	+ 6	54	+18	99	+43
	A	103	- 9.7	64	- 5.9	77	- 7.2	39	-15	126	+83
	T	105	- 8.6	72	+ 5.9	83	0	33	-28	129	+87
DOLITRONE	R	114		68		83		46		69	
(8 subjects)	C	121	+ 6.1	78	+14.7	92	+10.8	43	- 6.5	88	+28
	A	105	- 8.6	70	+ 3	82	- 1.2	35	-24	121	+75
	T	116	+ 1.8	80	+17.7	92	+10.8	36	-22	111	+61

R = resting
C = control study
A = acute effect
T = mean during 10 - 15 minutes after acute changes have stabilized.
SBP = Systolic Blood Pressure
DBP = Diastolic Blood Pressure
BP_m = Mean Blood Pressure
PP_m = Mean Pulse Pressure
PR_m = Mean Pulse Rate

tered (432 mg./M^2), all changes observed in these experiments were in the same direction and of the same order of magnitude as seen with buthalitone.

Compound 25398. The mean period of apnoea was 82 seconds with mean dose of 273 mg./M^2. Metabolic rate fell 25 per cent. Pulse rate rose 36 per cent

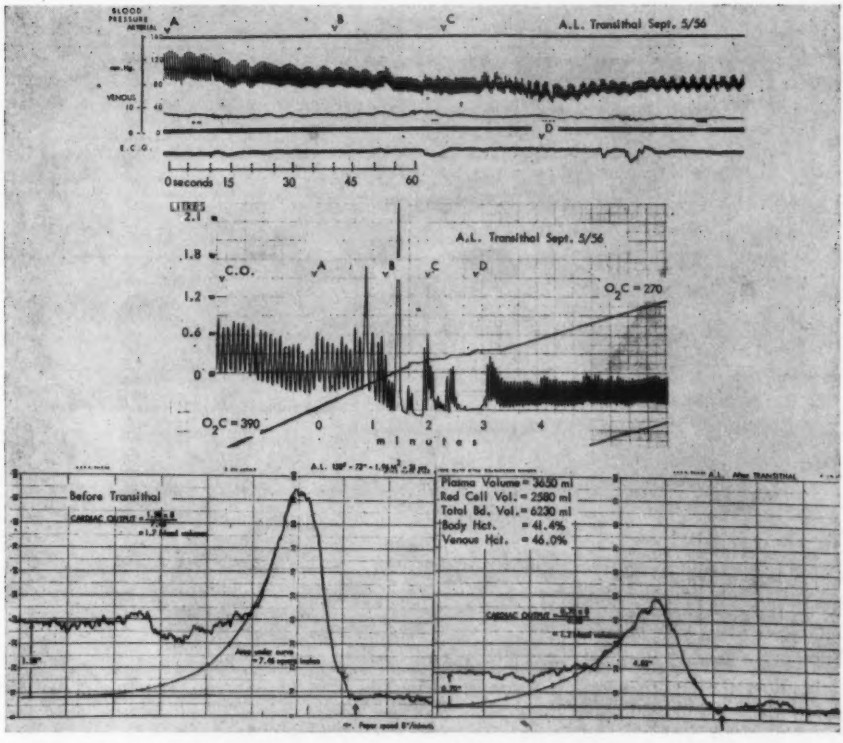


FIGURE 4. Tracing from a typical experiment showing simultaneous determinations of haemodynamic and respiratory parameters: *upper* shows arterial and venous pressure (ECG is too compressed in copy); *middle* shows respiration and oxygen consumption; *lower* shows cardiac output. "A" represents beginning of injection of drug. "B" represents beginning of injection of second sleep dose and "C" is end of injection. "C O" and "D" represent the control and test injections of Rhisa for the cardiac output estimation. On the respiration tracing the sloping line represents the oxygen consumption, which is noted before and after the injections. Method of computing the cardiac output is shown on the recording from the count-rate meter and Varian recorder.

while mean arterial blood pressure fell 9 per cent. There was a consistent fall in the mean venous pressure of 43 per cent. Cardiac output fell inconsistently to 15 per cent below resting levels while total peripheral resistance rose inconsistently to 17 per cent above resting levels. There was a 25 per cent fall in left ventricular work. These observed changes place this compound in the same class as thiopental and thiamylal, but with greater potency and greater depression of cardio-respiratory dynamics.

Dolitrone. The mean period of apnoea lasted 8 seconds with the mean dose of 512 mg./M^2, while metabolism was reduced 21 per cent. Pulse rate rose 39 per cent; mean arterial pressure fell 13 per cent. There was an inconsistent fall in the mean venous pressure of 22 per cent. There was a consistent fall in the cardiac output of approximately 20 per cent while the total peripheral

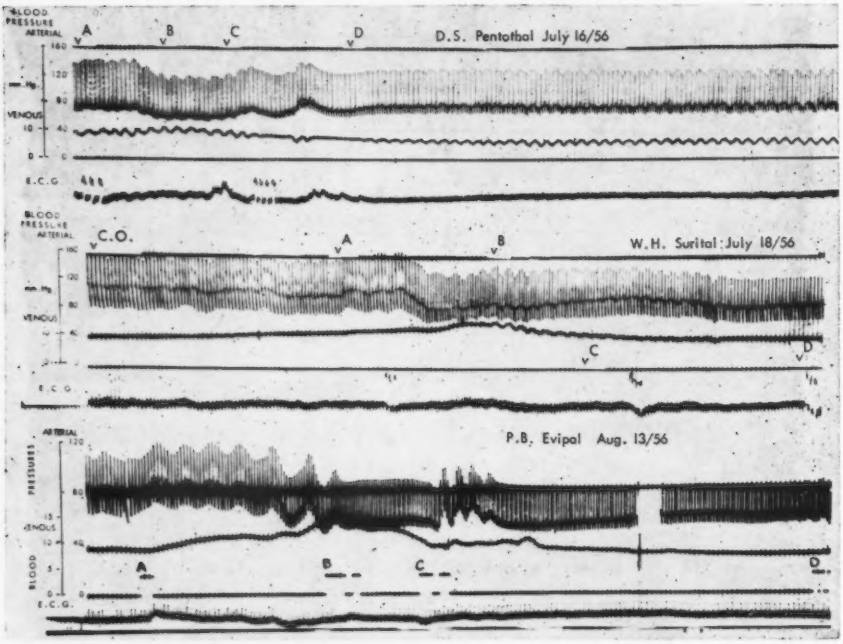


FIGURE 5. Haemodynamic response to thiopental, thiamylal and hexobarbital by a double dose. Note the rise in venous pressure preceding the start of injection, and then a fall to below the control level. Note the persistent depression in arterial blood pressure after the initial acute fall, which is greatest with hexobarbital and least with thiopental.

resistance tended to rise slightly. Left ventricular work decreased by 35 per cent.

The potency of this drug approximated that of hexobarbital very closely. Respiratory effects of this drug were also very similar to those seen with hexobarbital and buthaliton. However, the cardiodynamic depression by this drug was much greater than with both hexobarbital and buthalitone.

DISCUSSION

Blood Volume and Cardiac Output

The determination of total blood volume and cardiac output are critical values in this study. It is essential therefore to elaborate on their accuracy. It has been shown that "complete mixing" of an injected tracer substance such as Rihsa for determination of plasma volume occurs in the range of 4 to 15 minutes and that mixing times are discrete from the disappearance slope in most subjects (45, 46, 47). In this study a single 15-minute sample was taken in these normal subjects and was assumed to have complete mixing so that plasma volume would be calculated accurately. The determination of red cell volume by radioactive chromium is also a highly accurate determination according to Sterling and Gray

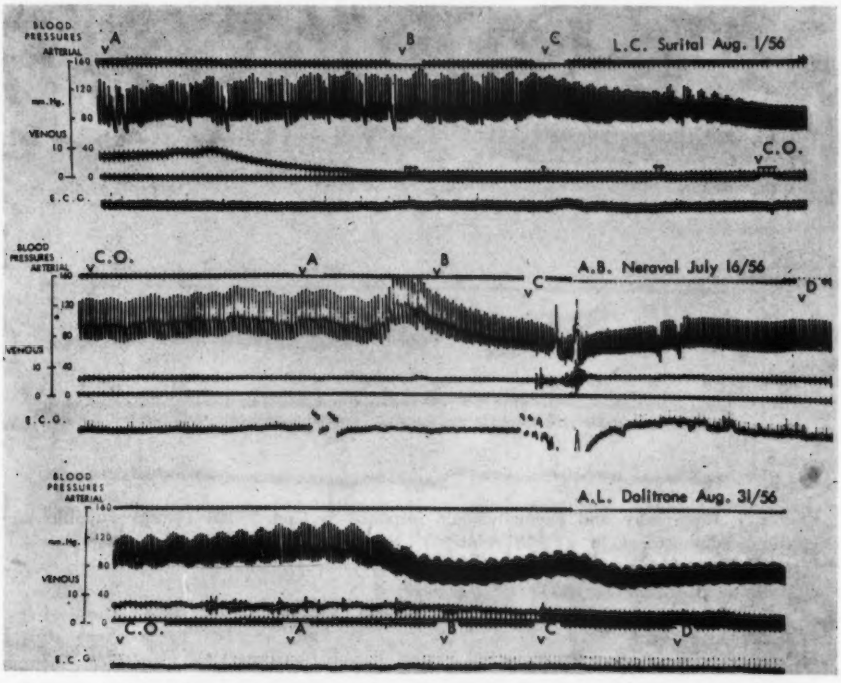


FIGURE 6. Haemodynamic response to thiamylal, methitural and Dolitrone. Note depression of arterial pressure for all three and marked fall in venous pressure with thiamylal and Dolitrone.

(22). The simultaneous measurement of plasma volume, red cell volume and venous haematocrit in the eight normal subjects in this study showed an almost constant ratio of body haematocrit to the venous haematocrit (0.90). These observations agree very closely with those of Hicks and associates (48) and those found in another study (27).

The determination of cardiac output by the injection method is based on the measurement of the varying concentration of the injected material as it passes through the heart. If a small volume of highly concentrated material is injected into the inflow tract, the average dilution of the material coming out from the heart will be a direct indication of the volume passing through the heart and causing this dilution. The measurement of the change of concentration during a definite interval permits the output to be expressed as volume of flow per unit time, as measured on a recorded cardiac dilution curve (45).

The main advantage of using iodine^{131} tagged serum albumin is that this concentration may be determined by gamma-ray assay. A continuous sampling of concentration without sample preparation may then be made, since the absorption in the blood or tissue is negligible. This obviates the laborious system of withdrawing arterial blood samples and assaying the samples, and makes

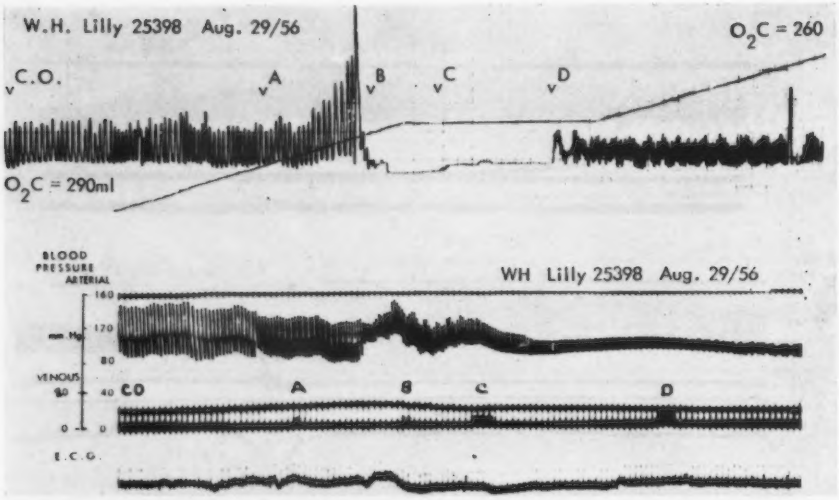


FIGURE 7. Respiratory and haemodynamic response to Cpd 25398 (Lilly) (double the sleep dose administered in a 2.5% solution). Note long period of apnoea and marked depression of respiration, arterial blood pressure and pulse pressure accompanied by marked tachypnoea and tachycardia.

accurate timing of the dilution curve more easily obtainable. Since all critical time measurements were made primarily within sixty seconds (including the time from the moment injection started), and the loss of serum albumin from the vascular system is not more than about 3 per cent for the first ten minutes following injection, the method is entirely satisfactory for precise measurement of the period being studied and has a high order of accuracy compared to the dye injection method (49, 50).

Because the injected material is diluted very rapidly, it is necessary to employ a detector of the highest sensitivity. A highly collimated crystal detector (scintillation counter) with high sensitivity to gamma radiation is therefore essential for these estimations. Such a detector must be directed over the area of the chest where the least interference from other blood flows is located, namely the first left interspace of the chest, adjacent to the sternum (51). The dilution curve or the change in concentration of the diluted material in the blood is recorded by a scaler and counting rate-computer combination and inscribed automatically by a direct writing recorder. A fast response time-counting rate meter is also satisfactory, but the scaler-computer combination eliminates the memory effect of the rate meter and allows a lower counting rate and dose to be used. Successful repeated measurements can be made with 25 to 75 microcuries (52, 53, 54).

The dilution curve has the same general form as that seen with Evans Blue dye. There is characteristically a rapid initial rise as the bulk of the radioactivity passes the counter site, followed by a steep fall to a partially super-

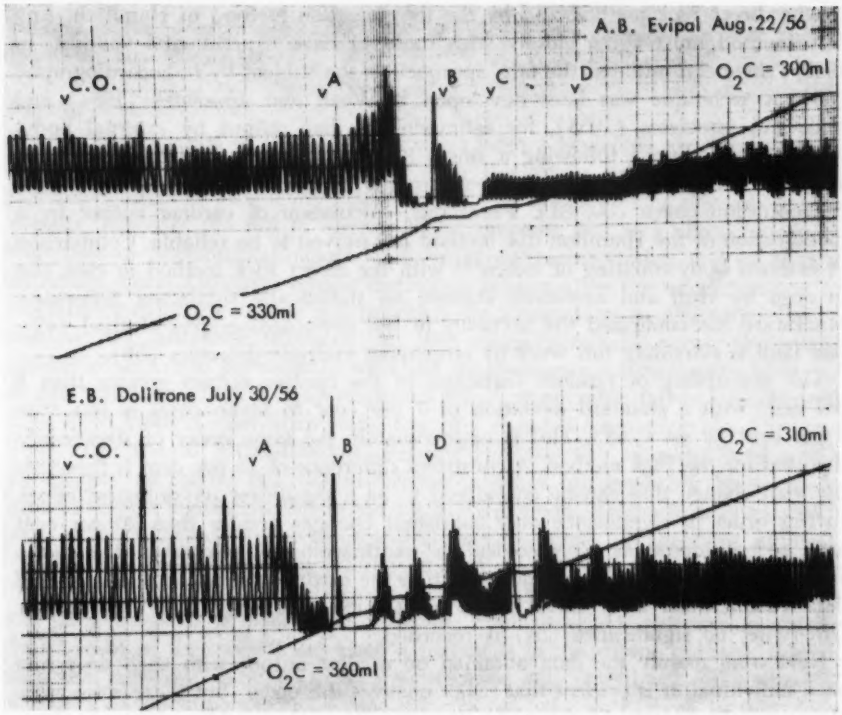


FIGURE 8. Typical respiration tracings obtained with hexobarbital and Dolitrone. Note the similarity in response with these two agents.

imposed small recirculation curve. To correct for the recirculation effect, the curve is extrapolated exponentially from the point *b* (Fig. 2). Since the same total injected material (I) must come out of the heart as was injected into the inflow tract, this quantity of injected material must be equal to the product of the flow rate (F) multiplied by the concentration of the tagged material (c) in the blood integrated over the entire time of the primary circulation. This is represented by the equation:

$$I = \int_0^\infty F\,c\,dt$$

and if F, the flow rate or cardiac output, is constant,

$$I = \int_0^\infty F\,c\,dt, \qquad \text{where } \int_0^\infty$$

represents the area under the primary circulation curve and the extrapolation line. This area is equivalent to area A and area B shown in Figure 2. Since the injection dose I is equivalent to the final dilution C_f multiplied by the volume V, the expression for the cardiac output is: $F = C_f V/(A+B)$.

Much has been reported on the accuracy of cardiac output determinations

by the direct Fick method and by the dye injection method of Hamilton. Any new method must agree closely with these to have experimental validity. In 1949, Prinzmetal initiated the new approach to the subject by radiocardiography (55). A technique was later developed by Veall and associates (1954) and Huff and associates (1955), for estimating cardiac output by external body-counting of iodine^{131} following a single injection, using a well-collimated and shielded scintillation detector placed over a fixed site for recording a time concentration curve (30, 31). From this, calculation of cardiac output by a modification of the Hamilton dye method has proved to be reliable. Comparison of external body-counting of iodine^{131} with the direct Fick method in men and in dogs by Huff and associates showed no statistically significant difference. MacIntyre has confirmed the accuracy of the radiocardiography method (47), and Huff is extending this work by employing multiple detectors (56).

The probability of random variations in the cardiac output greater than 5 per cent with a standard deviation of 7 per cent in seven cases is less than 5 per cent ($P = <.05$). This is approximately the same order of significance reported for the Fick method. A consistent difference of 15 per cent is therefore the least change that can be considered to be a significant physiological effect. In this order of significance only consistent changes greater than 20 per cent may be considered as physiological or pharmacological effects on the stroke volume and other parameters derived from the cardiac output. In the tabulated data (Tables X–XVI), the P value for significant changes only are shown. Otherwise, no significance (ns) is recorded.

Reviewing mainly the data obtained on cardiac output with each drug and each individual, it is evident that major changes did occur, but these were more often not consistently in the same direction. Van Harreveld and Shadle have also noted such changes in haemodynamics by barbiturates and point out that the great complication is produced in the normal circulation by the activity of circulatory reflexes and hormonal mechanisms which affect a number of parameters of the circulatory apparatus simultaneously (57). The analysis of such changes may therefore become very difficult. It is essential, especially in the study of the regulating mechanism of the circulation, to record simultaneously as large a number of dependent variables as possible. These give a more reliable clue to major parameters affected, and the direction of such change. It will be possible only in rare instances to draw conclusions about the mechanisms of circulatory effects from the changes of a single dependent variable like the cardiac output.

Arterial Blood Pressure

With few exceptions, every drug that was studied in these experiments caused an initial sharp fall in blood pressure which lasted at least a few minutes. This fall was followed by a gradual rise to a lesser depressed level, where it remained until the subject was fully conscious. The initial fall may be considered as primary depression of vasomotor tone, followed rapidly, in most instances, by partial reflex restoration. However, persistent mild depression lasted beyond the time the subject was awake, indicating that some depressant is probably

present in the circulation in active concentration. This alteration is well known in clinical anaesthesia (58).

Venous Blood Pressure

The determination of venous pressure has been a neglected aspect of haemodynamic effects of anaesthetic drugs even though its role in surgical shock has been suggested frequently. Moon found that fall in venous pressure, which persists, precedes the fall in arterial blood pressure that is a characteristic of traumatic or haemorrhagic shock—both in experimental studies and in clinical situations (59). Although venous distension is seen after the administration of vasodilator drugs, it is not accompanied by a decrease in circulating blood volume (27). However, it is seen also with many anaesthetic agents (especially diethyl ether), and particularly with the intravenous anaesthetics, as observed in this study, and then it is accompanied by a considerable fall in venous pressure. Such a fall is most likely indicative of a reduced circulating blood volume (60). The fall in arterial blood pressure and the rise in pulse rate which accompany or follow this fall in venous pressure can probably be taken as indicative of a significant fall in the circulating blood volume to a level which may produce hypoxia to the heart and other vital organs (brain, liver, kidney).

Although these changes in arterial and venous pressure were well tolerated by the healthy subjects in this study, a critical disturbance is often evident in the patient who is in poor general health. Because venous pressure is usually found to be at its lowest level when a patient is in the supine position, a great fall from this level assumes greater significance and should not be ignored as a sign of advancing shock. The venous pressure changes observed in this study are therefore highly significant and probably symptomatic of a derangement of haemodynamics which is less obviously indicated by arterial hypotension, by tachycardia and by an occasional minor electrocardiographic alteration.

It was of interest to observe a sudden significant rise in the venous pressure in most experiments immediately upon the subject becoming aware that drug injection was about to begin. This reaction is clearly evidence of the effect of anxiety on venous pressure. The rise may be seen in Figures 5, 6 and 7, and is shown on the tables by the range of venous pressures in the control record.

Heart Rate and Electrocardiogram

There was invariably a marked increase in heart rate above the resting and control levels with all the drugs. This affect was most apparent with Dolitrone, Compound 25398 and hexobarbital. However, no gross disturbances of the PQRST complexes were evident with any of the drugs. Although continuous electrocardiographic recordings were taken throughout this study, it was known that they would be inadequate for estimating the degree of myocardial depression produced by barbiturates, since severe depression of contractile function usually does not lead to any remarkable electrocardiographic changes.

In animal studies, Daniels and associates observed that heart failure induced by barbiturates alone is primarily the result of their negative inotropic action. However, suppression of autonomic rhythmicity and conduction is responsible

for cardiac arrest when contractility is preserved by norepinephrine infusion, and under these circumstances arrest occurs when excitability is relatively unimpaired. They stated that the ability of noradrenaline and isoproterenol to antagonize barbiturate intoxication is probably the result of cardiac stimulation and could not be attributed to peripheral vasoconstriction. They observed further that when these drugs fail to antagonize cardiac depression induced by barbiturates, there is atrio-ventricular block and suppression of sinus pacemaker activity (61).

From the work of Brodie and associates (62) it is evident that the degree of impairment of cardiovascular function is initially determined by the concentration in the blood of the intravenous anaesthetic, and that the metabolic inactivation is not sufficiently rapid to affect the results significantly at the rates of administration employed clinically. This statement unquestionably applies in a similar, but distinguishable degree, to each of the drugs tested in this study.

Since clinical limitations must be respected, we always turn to *animal data* for guidance and infer the sequence of changes which may occur in man (63–72). In this respect, it is unfortunate that only a few of the small number of clinical studies (20, 38) that have been reported were carefully controlled by limiting the drugs administered (73, 74, 75).

The cardiovascular lethal dose of thiopental occurs in dogs with approximately 160 mg. per kg. when this agent is infused at the rate of 75 mg. per kg. per minute (64). Variation in the extent of redistribution of thiopental into fat may account for some of the variations in the cardiovascular lethal doses at different infusion rates. This probably applies also to different concentrations of injected drugs. The sequence of events leading to cardiovascular failure in continuous infusion experiments have been worked out in the dog. The following sequence is seen consistently: onset of hypotension soon after infusion is started, progressing rapidly to severe hypotension as the infusion continues. The rate of injection influences the rate of collapse and at critical rates irreversible cardiovascular collapse occurs in spite of artificial respiration. The compensatory tachycardia is not sufficient to compensate for hypotension. The heart rate begins to fall rapidly in the terminal stages. T-wave flattening is the earliest significant electrocardiograph change, then further flattening and depression of the ST segment occurs. *These may not appear until very low blood pressures are reached.* Daniels pointed out that barbiturates in quantities not much larger than those producing respiratory arrest, produced marked hypotension in the dog even when hypoxia is prevented (61). Employing a "mathematical model of the circulation" Van Harreveld and Shadle demonstrated that the heart is the primary site of cardiovascular depression due to barbiturates rather than any central or peripheral vasodilating effect (57). If myocardial depression is the principal mechanism whereby cardiovascular function is impaired during barbiturate intoxication, it seems reasonable that much smaller doses of barbiturate may affect cardiac function adversely under appropriate circumstances. This could explain the brief episodes of hypotension often seen with small intravenous doses of barbiturates in intact dogs or in patients. The transitory nature of such effects are attributed to compensatory mechanisms, which are present

until reflex nervous activity is eliminated. However, a study of anaesthetic doses of pentobarbital in dogs attributes hypotensive effects to peripheral vaso-dilatation with *no decrease in cardiac output* (67). In a study of thiopental anaesthesia in man, a decreased cardiac output with peripheral vasoconstriction and pooling of blood but with *no* change in arterial pressure was observed. The data from this study confuse the question somewhat since the patients received premedication with therapeutic doses of opiates, the thiopental was administered in a dilute drip, and electroencephalographic levels rather than actual drug doses were primarily considered. Administration by a dilute drip technique permits compensatory mechanisms to come into play and usually prevents the appearance of acute changes in haemodynamics until very large doses have been administered. The consistent decreases in cardiac output seen by these experimenters therefore is difficult to explain, unless they actually administered very large doses of thiopental, or their patients had impaired cardiac function which was not detected preoperatively. In addition, a potentiating depressant effect on the heart by drug combinations was not ruled out (75).

That anaesthetic levels of thiopental actually do depress cardiac function, *if compensatory changes cannot occur*, has been shown with the heart-lung preparation by Price and Helrich. They demonstrated that changes in slope of the curve relating cardiac output to right arterial pressure caused by thiopental may be used as an index of cardiac depression (76). In the studies of Daniel, despite the infusion of epinephrine in animals, anaesthetic doses of thiopental still impaired cardiac function (61).

From work with animals it seems evident that doses of intravenous barbiturates which produced respiratory arrest for more than a brief period directly depress cardiac function. Artificial respiration and stimulation of the central nervous system as by amphetamine alone does not counteract this effect. Therefore, cardiac stimulants such as sympathomimetic amines and the catecholamines would seem to be indicated in animals.

In applying such information to man it is important to realize that it is essential to limit the use of the short-acting barbiturates to the "sleep dose" with the drug *which does not cause more than a few seconds of apnoea.* It would be best to employ an agent which produces hypnosis and some analgesia entirely without apnoea and employ supplementary anaesthetic drugs if greater analgesia and muscle relaxation are necessary for the operative procedure. In this way, cardiovascular function may be preserved in an optimal way without the need for supportive drugs.

Since extensive comparative data in humans are lacking for the newer short-acting barbiturates, one must begin with such data as reported in this study and compare them with reports on animal studies and human studies of the individual drugs. From these one must attempt to infer those data which are applicable to man. Thereafter, clinical data must be collected carefully, with documented notes on relative potency, duration of sleep for various dose levels, rate and concentration of drug administration, rate of onset of sleep and rate of recovery (77). The latter must be related to valid criteria, such as response to name, lucidity, absence of diplopia and dizziness, and ability to concentrate

mentally. Since repeated doses may be necessary under clinical circumstances, note must be made of "acute" tolerance, cumulation or tachyphylaxis. The degrees of respiratory depression and cardiac acceleration are vital parameters to the clinical anaesthetist and must be diligently recorded. Cardiac arrhythmias, such as ectopic beats and bigeminal rhythm, are easily missed, but these must be carefully sought. Of importance also is the incidence of vagus-like reflexes such as coughing, hiccoughing, sneezing and laryngeal spasm. The protective effect of premedication with belladonna derivatives or a specified technique of anaesthetic induction on these undesirable reactions or reflexes should be sought and clarified. Last but not least, the incidence of inflammatory reactions in the veins must be carefully observed, as must neuromuscular responses to these drugs (twitching, shivering and involuntary spastic movements). Even if an agent fulfils all the desirable anaesthetic criteria, rigidity or twitching in a patient frequently suggests acute hypoxia or toxic reactions in the nervous system and is most undesirable, even if analgesia and hypnosis are optimal.

The data from this study indicate thaf as far as duration of sleep is concerned for double the sleep dose, the drugs may be divided into two classes: those with over 30 minutes of sleep and more than 20 seconds of apnoea on induction; and those with less than 20 minutes of sleep and less than 10 seconds of apnoea. This division is most evident when the duration of apnoea and sleep are computed on an equal dose basis (Table XIX). In the first group, Compound 25398 is by far the most potent hypnotic, and has the marked disadvantage of causing a prolonged period of apnoea, hypotension and tachycardia. There is essentially no difference between thiopental and thiamylal, although the latter is a somewhat more potent hypnotic, without prolonging the period of sleep, and produces less apnoea on the basis of equal dose administration. The second group of drugs consists of methitural, Dolitrone, hexobarbital and buthalitone. Methi-

TABLE XIX

ANAESTHETIC EFFECT OF INTRAVENOUS ANAESTHETICS

(Calculated on the basis of 500 mg./M^2 of body surface area)

DRUGS	Duration of Apnea seconds	Duration of Sleep minutes	2 x Sleep Dose mg.
LILLY 25398	150	42	273
SURITAL	29	33	402
PENTOTHAL	36	34	442
NERAVAL	7	19	432
DOLITRONE	8	12	512
EVIPAL	7	12	517
TRANSITHAL	9	5	637

tural is the most potent of this group and is very similar to thiopental with respect to the double sleep dose. However, the duration of hypnosis is only approximately 60 per cent of that for thiopental, whereas the period of apnoea is the shortest seen in the whole group with respect to both duration of sleep and the double sleep dose. It would appear from the above findings that methitural has particular advantages over the other three drugs in that group, if hypnotic potency is desired for short operative procedures, while very short procedures would be best carried out under buthalitone as originally suggested by Weese (69); and Dolitrone has the one advantage of having a definite analgesic effect of its own (13). However, both buthalitone and Dolitrone have a disturbing side effect (twitching or spontaneous movements) which is difficult to tolerate, and Dolitrone has a higher incidence of venous irritation than the other agents (13). Compared to thiopental methitural produces less cardiac acceleration, but the same degree of hypotension, and more vagal-type reactions (coughing, sneezing and hiccoughing) on induction. In animals, a far greater incidence of cardiac arrhythmias (ectopic beats and bigeminal rhythm) is seen with methitural. Arrhythmias may become evident in clinical anaesthesia with methitural when specifically sought, unless premedication with belladonna derivatives adequately prevent their occurrence. No tolerance or cumulative action for thiopental (25 mg./kg.) and methitural (45 mg./kg.) after daily administration for 30 days has been reported (70). There is probably also no tolerance or cumulative action for the other drugs studied.

All the drugs significantly depressed oxygen consumption except hexobarbital, with the greatest decrease produced by thiopental, and the least by Dolitrone. This effect is common to all anaesthetics in varying degree (78). The pulse rate was significantly increased by all the drugs except methitural, with the greatest increase by Dolitrone (39 per cent) and Compound 25398 (36 per cent) and the least by buthalitone (10 per cent). All the drugs depressed the blood pressure

TABLE XX

SUMMARY OF SIGNIFICANT MEAN PERCENTAGE CHANGES IN HAEMODYNAMICS AND METABOLISM DURING ACUTE STUDY

	Pentothal	Surital	Evipal	Transithal	Neraval	Lilly 25398	Dolitrone
Metabolic Rate	-33	-29	-6	-23	-25	-25	-21
Mean Pulse Rate	+16	+14	+28	+10	+3	+36	+39
Mean Arterial Pressure	-17	-7	-12	-15	-17	-9	-13
Mean Venous Pressure	-23	-42	-17	-17	-39	-43	-22

to a degree which did not vary greatly among the seven agents. Venous pressure was also reduced by all the drugs by at least 15 per cent, with the least changes observed with hexobarbital and buthalitone (Table XX). None of these changes approached the degree of disturbance which is observed with high spinal anaesthesia (79, 80).

Summary and Conclusions

The problems of comparing several anaesthetics are reviewed with particular reference to the effects of premedication, the intrinsic activity of drugs and their affinity for certain tissues and the effect of multiple drug interaction. The physiological and pathological states of those patients who are used as subjects of such studies are essential factors to be clearly determined. The effects of acute tolerance, cumulation and tachyphylaxis were also cited as factors to be considered.

A controlled study of respiratory and haemodynamic parameters was carried out on eight young healthy male subjects in order to determine the principal and statistically significant effects of thiopental, thiamylal, hexobarbital, buthalitone, methitural, Compound 25398 and Dolitrone.

Resting vital signs were initially obtained as well as other vital statistics. Basal metabolism and cardio-respiratory parameters were determined from nomograms related to the resting values. These data provided the base line for all control and experimental data. Plasma volume and red cell volume were initially determined simultaneously with radioactive iodinated human serum albumin (I^{131}) and radioactive chromium^{51}, employing the dilution principle. These were checked against venous haematocrit determinations.

Respiration data were obtained on a recording spirometer which also recorded oxygen consumption. Cardiovascular data (arterial and venous blood pressure) were recorded via intra-arterial and intravenous needles attached to Statham strain gauges, oscilloscopes and a photographic recorder. The pulse rate and electrocardiogram (lead 2) were also recorded on this system. The cardiac output was estimated by external body-counting of I^{131} following single injections of Rihsa, using a shielded scintillation detector directed over a fixed site on the chest where tissue circulation was minimal, in order to measure primarily the blood flow in the aortic arch. Mean circulation time and cardiac output were derived from measurements on the recordings, and stroke volume, total peripheral resistance, left ventricular work and intrathoracic blood volume were computed from the above data.

All data were analysed for mean alterations, and statistical significance was computed to determine the probability (P value) of random variation by the method of the Fisher t-test.

The accuracy of the technical procedures employed was reviewed, with particular reference to the newer methods for estimating blood volume, cardiac output and mean circulation time, and was found to compare reliably with that of tried and recognized methods. The limitations of clinical studies were also discussed, and data from animal studies were reviewed with a view to supplementing information on the toxicity and cumulative effects of these drugs.

A conservative evaluation of the results was essential in this study since it was assumed that deviations of values were normally distributed, and that the study dealt essentially with the healthiest type of subjects one ever encounters in clinical practice. The authors also felt, as noted by Johnson and Van Harreveld, that so many factors are involved in cardio-respiratory regulation, both before and during anaesthesia, that one must be extremely cautious in stating which factor is primarily involved in a change. One must therefore avoid conclusions from individual changes and base critical evaluation on consistent and statistically significant changes in a "homogenous" group, and then perhaps apply these data to an individual.

From the experiments, the seven intravenous anaesthetics studied could be divided into two main groups: those that produced a prolonged depression of respiration and circulation; and those that produced a brief depression of these parameters. Compound 25398, thiamylal and thiopental belong to the first group, while methitural, Dolitrone, hexobarbital and buthalitone belong to the second. All the drugs except hexobarbital depressed oxygen consumption. Tachycardia was a significant finding with all the drugs except methitural and acute hypotension (arterial and venous) was a consistent finding with all the drugs. Considering all the parameters, myocardial depression was induced by the first group, but this was not consistently manifested by a decrease in the cardiac output.

From this investigation, it is difficult to choose among the agents and state which disturbs human physiology to the least extent while providing clinically adequate hypnosis. It is only possible to state the advantage of a particular agent with reference to a specific patient, a specific type of operation and a specific clinical situation. On this basis, extensive clinical experience with one agent is probably the most reliable method of managing most situations, for then the problem comes down to a matter of dosage, concentration of the drug, and rate of its administration.

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Résumé

Nous avons étudié les problèmes que pose la comparaison de plusieurs anesthésiques en prêtant une attention particulière aux effets de la prémédication, à l'activité intrinsèques des médicaments et à leur affinité pour certains tissus, puis, enfin, à l'effet de l'interaction de plusieurs médicaments. Il nous faut donner des précisions sur la condition physio-pathologique des malades chez qui on a

employé ces médicaments pour les étudier. Nous avons également mentionné comme facteurs non négligeables: la tolérance aiguë, l'accumulation et la tachyphylaxie.

Nous avons fait, chez huit jeunes sujets mâles en santé, une étude, avec contrôles, des paramètres respiratoires et hémodynamiques pour tabuler les effets principaux et les effets présentant un intérêt statistique sur le thiopental, le thiamylal, l'hexobarbital, le buthalitone, le methitural, le composé 25398 et le dolitrone.

Nous avons d'abord cherché les signes vitaux à l'état de repos de même que d'autres statistiques vitales. Le métabolisme de base et les paramètres cardio-respiratoires ont été tirés des nomogrammes donnant les valeurs à l'état de repos. Ces résultats nous ont fourni les bases pour les données de contrôle et expérimentales. Les volumes plasmatique et globulaire ont été recherchés simultanément au début avec le sérum albumine humain iodé radioactif (I^{131}) et le chromium radioactif^{51} en employant le principe de dilution. Ces deux résultats ont été comparés aux déterminations de l'hématocrite sur le sang veineux.

Au sujet de la respiration, les données ont été obtenues au moyen d'un spiromètre enregistreur renseignant également sur la consommation d'oxygène. Les renseignements sur le système cardiovasculaire (pression artérielle et veineuse) ont été obtenus et enregistrés au moyen d'aiguilles placées dans les artères et dans les veines et reliées au manomètres Statham, aux oscilloscopes et à un enregistreur photographique.

Le rythme cardiaque et l'électrocardiogramme (en deuxième dérivation) ont également été enregistrés sur le même système. Le débit cardiaque a été évalué de l'extérieur de l'organisme en repérant l'I^{131}, après une seule injection de Rihsa, et en promenant un détecteur à champ scintillant au-dessus d'un endroit précis sur le thorax où la circulation tissulaire est réduite de façon à obtenir principalement le débit sanguin de la crosse aortique. La moyenne du temps de circulation et le débit cardiaque ont été obtenus de ces enregistrements, et le débit systolique, la résistance périphérique totale, le travail du ventricule gauche et le volume de sang intrathoracique ont été calculés d'après ces données.

Tous les résultats ont été analysés pour trouver la moyenne des modifications et la signification statistique a été calculée pour obtenir la probabilité (la valeur P) de variation isolée par la méthode de Fisher.

Nous avons contrôlé la précision des techniques employées, plus particulièrement les techniques nouvelles pour mesurer le volume sanguin, le débit cardiaque et la moyenne du temps de circulation et nous pouvons affirmer que les résultats sont comparables à ceux obtenus par d'autres techniques éprouvées et reconnues. Nous avons également discuté des limites des études cliniques et les résultats des études faites sur l'animal ont été étudiés dans le but d'obtenir des renseignements additionnels sur la toxicité et les effets cumulatifs de ces médicaments.

Dans cette étude, il était essentiel d'avoir une évaluation conservatrice des résultats car nous présumions que la déviation des résultats était répartie normalement et que l'étude a été faite sur des sujets les plus en santé qu'on puisse trouver en clinique. Les auteurs ont également eu la conviction, comme l'affirment Johnson et Van Harreveld, qu'il y a tellement de facteurs impliqués dans

le maintien de l'équilibre cardiorespiratoire, aussi bien avant que pendant l'anesthésie, qu'il faut être très prudent avant d'affirmer que tel ou tel facteur est primitivement responsable d'un changement. Conséquemment, il faut éviter de conclure d'après des changements individuels et baser une évaluation critique sur des changements considérables et d'importance statistique observés sur un groupe homogène et après, peut-être, comparer ces données à l'individu.

D'après ces expériences, on peut diviser en deux groupes les sept agents anesthésiques étudiés, il s'agit d'agents administrés par voie endoveineuse: ceux qui ont entraîné une dépression prolongée de la respiration et de la circulation et ceux qui ont entraîné une brève dépression sur ces paramètres. Le composé 25398, le thiamylal et thiopental appartiennent au premier groupe, tandis que le methitural, le dolitrone, l'hexobarbital et le buthalitone appartiennent au dernier groupe. Tous ces médicaments diminuent la consommation d'oxygène à l'exception de l'hexobarbital. On a observé une tachycardie importante à la suite de l'administration de tous ces médicaments à l'exception du méthitural et une hypotension marquée (artérielle et veineuse) à la suite de l'administration de chacun de ces médicaments. En analysant tous les résultats, on note que les médicaments du premier groupe ont causé une dépression myocardique mais elle n'a pas toujours été accompagnée d'une diminution du débit cardiaque.

Après cette enquête, il demeure difficile d'affirmer lequel de ces agents cause le moins de changement dans la physiologie humanie tout en procurant une hypnose adéquate cliniquement. Il nous est possible tout au plus de mentionner la supériorité d'un agent en particulier pour tel ou tel malade, ou encore pour telle sorte d'opération ou pour une situation clinique particulière. En se basant sur ces faits, nous pouvons affirmer qu'une longue expérience clinique avec un agent demeure probablement le facteur le plus sûr pour contrôler toutes les éventualités, car le problème se résume à une question de dosage, de dilution de médicament et de vitesse d'administration.

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BUTHALITONE SODIUM ANAESTHESIA: DRUG CONSUMPTION AND SERUM PROTEIN STUDIES*

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AT THE TIME of their introduction, the early thiobarbiturates, derivatives of barbituric acid, appropriately deserved the designation of "ultra-short-acting" anaesthetics. Nevertheless, for office, dental or out-patient interventions, their effect still lasts longer than desirable. They also fall short of ideal by increasing vagal irritability and producing central and myocardial depression.

Weese and Koss (1) in introducing buthalitone sodium (Baytinal), a new thiobarbiturate, claimed that this agent had a shorter action and produced less respiratory depression. Extensive clinical trials in Europe (2–14) tend to confirm these views, but American experience with the drug is so far limited.

Buthalitone sodium is the sodium salt of 5,5-allyl-(2′-methyl-propyl)-thiobarbituric acid. It is known in Great Britain at "Transithal" and on the European continent as "Baytinal."

We recently had the opportunity to use buthalitone sodium and we report here our findings.

MATERIAL AND METHODS

Thirty-seven patients undergoing uterine curettage were the subjects of our study. The material was selected only in so far that patients with recent massive haemorrhage or marked debility were excluded from the trials. All subjects received routine premedication and buthalitone sodium was administered in a 5 per cent solution, usually through the subclavian vein (15). As soon as the eyelid reflex disappeared, high flow nitrous oxide (3:1) was administered by mask and respirations were vigorously assisted or controlled. Supplementary buthalitone sodium was given as necessary and the time of administration recorded. At the end of the intervention, note was made of the time when the subjects reacted to a standard stimulus, pinching of the trapezius muscle. The duration of anaesthesia or anaesthesia time was defined as the interval between the initial administration and the reaction to stimuli. The time when the patients were first able to correctly state their age was also noted.

From 23 of the 37 patients blood samples were taken immediately prior to induction and at the end of the procedure. Haematocrit, serum protein and protein distribution were determined on every sample, using standard clinical laboratory techniques of Wintrobe, nephelometry and filter paper electrophoresis respectively. The filter paper strips were evaluated with a semi-automatic scanning device (Spinco Analytron).

Earlier data from 24 curettages, where anaesthesia was performed by the same

*This study was supported by a grant from Poulenc Ltd., Montreal.

†From the Department of Anaesthesia and the Chemical Laboratories of Notre-Dame Hospital, Montreal.

anaesthetist using an identical technique but with thiopentone as the intravenous agent, served as a basis for comparison in the drug consumption studies.

Results

The consumption of buthalitone sodium as compared with that of thiopentone is given in Table I. Measures of recovery from anaesthesia are shown in Table II. In Table III are presented the serum protein and haematocrit values before and after anaesthesia. The statistical data relevant to protein changes and to the

TABLE I

Drug Consumption for Curettage in Premedicated Patients
(using buthalitone: B, 37 cases; or thiopentone: T, 24 cases)

	B			T			$V\sigma$		σ_M		
	M		σ	M		σ	B (%)	T (%)	B	T	t
Age (years)	37	±	13	37	±	12	35	32	2.1	2.4	
Weight (lb.)	129	±	23	133	±	25	18	19	3.8	5.3	
Anaesthesia time (min.)	22	±	8	26	±	8	36	30	1.3	1.6	1.94
Thicbarbiturate (mg.)	652	±	269	415	±	164	41	40	42.5	34.1	4.3
Mg./lbs.	5.1	±	2.0	3.2	±	1.3	39	41	0.33	0.28	4.4
Mg./min.	30.1	±	15.6	16.8	±	8.6	52	51	2.56	1.79	5.5
Mg./lbs./min.	0.23	±	0.12	0.13	±	0.07	52	54	0.0020	0.0014	42.0

TABLE II

Rate of Recovery from Buthalitone Sodium

	M		σ
Anaesthesia time (from initial administration to reaction to stimuli)	22.0	±	8.0 min.
Duration of final dose (from last administration to reaction to stimuli)	9.4	±	4.3 min.
Reaction time (from end of surgery to reaction to stimuli)	2.3	±	1.3 min.
Answering time (from end of surgery to stating age)	6.0	±	4.2 min.

TABLE III

Serum Protein and Haematocrit Values: Standard Errors (σ) and Coefficients of Variation (V_σ) before and after Buthalitone Na Anaesthesia
(23 cases)

	Before				After			
	M		σ	V_σ (%)	M		σ	V_σ (%)
Haematocrit (%)	39.3	±	3.7	9	39.0	±	3.7	9
Serum protein (gm./l)	64.6	±	7.5	12	62.7	±	7.0	11
Albumin	33.3	±	6.5	19	32.1	±	4.3	13
α_1	2.8	±	0.7	25	3.0	±	0.6	20
α_2	6.9	±	1.3	19	6.9	±	1.7	25
β	9.6	±	1.9	20	9.2	±	1.8	20
γ	11.9	±	2.5	21	11.5	±	2.1	18

TABLE IV

STATISTICAL CHARACTERISTICS OF SERUM PROTEIN AND HAEMATOCRIT CHANGES FOLLOWING BUTHALITONE ANAESTHESIA
(23 cases)

	B	A	Δ	σ_M	t	Δ'	σ_M'
	(preop.)	(postop.)	(B–A)	$\sqrt{\frac{N\Sigma x^2-(\Sigma x)^2}{N^2(N-1)}}$	$\frac{\Delta}{\sigma_M}$	$\frac{A}{B}\times 100$	$\frac{\Delta'}{t}$
Haematocrit (H)	39.3%	39.0%	0.3%	0.091	3.30	1.0	0.30
	gm./L	gm./L	gm./L				
Protein (P)	64.6	62.7	1.9	0.502	3.00	−3.0	0.79
Albumin (A)	33.4	32.1	1.3	0.396	3.28	−4.0	1.22
α_1	2.8	3.0	−0.2	0.092	2.17	+7.1	3.27
α_2	6.9	6.9		0.119	0.17	−0.4	2.35
β	9.6	9.2	0.4	0.182	2.20	−4.7	2.14
γ	11.9	11.5	0.4	0.229	1.75	−3.0	1.71

Statistical significance (t) of the variations between the different protein fractions (at P.05 for 23 samples, $t = 2.07$).

A–α_1	*3.18*					
A–α_2	1.29	α_1–α_2	1.79			
A–β	0.78	α_1–β	*3.00*	α_2–β	1.33	
A–γ	0.48	α_1–γ	*2.74*	α_2–γ	0.84	β–γ 0.62

significance of variations among the individual protein fractions are tabulated in Table IV.

Percentage changes of the protein fractions and the standard deviations of the mean are plotted in Figure 1.

DISCUSSION

As seen in Table I, buthalitone sodium is indeed a shorter-acting agent than other thiobarbiturates now in common use. The drug consumption is significantly higher than with thiopental, regardless of the way in which it is expressed. Nevertheless, post-anaesthetic recovery occurs rapidly after discontinuation of the anaesthetic. It should be emphasized that these results were obtained in hospitalized, premedicated subjects. In a small number of out-patients who were given buthalitone sodium without premedication for minor procedures, we found the recovery even faster, in accordance with claims of European investigators.

It was our clinical impression that whereas in the thiopental series respiration of the subjects could be controlled almost routinely, this was next to impossible in the buthalitone sodium group. We take this as an indication of less respiratory depression and further experiments are in progress to objectivate this finding.

It may be argued that the data on recovery time show recovery from nitrous oxide anaesthesia rather than recovery from buthalitone sodium and that the interventions were carried out more under nitrous oxide than under buthalitone sodium anaesthesia. Even if this were conceded, the comparison with thiopental would still remain valid since identical techniques were used. The difference between the mean anaesthesia times of the two groups argues against such an assumption. This difference is "probably significant" in the statistical sense (Table

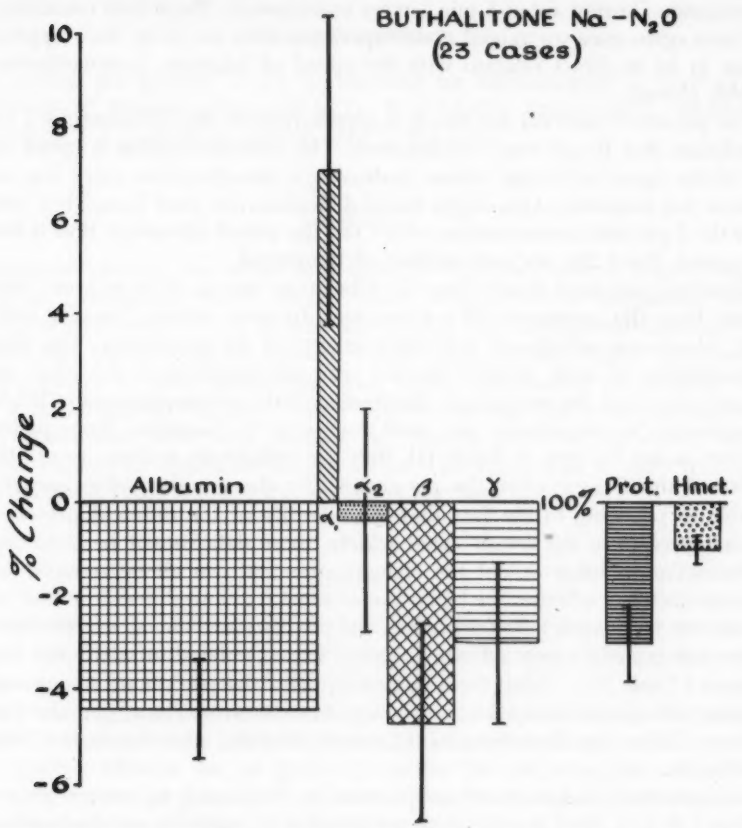

FIGURE 1. Variations in haematocrit, serum protein and protein fractions following buthalitone Na anaesthesia. The variations are expressed as percentage of the initial values, the vertical lines represent

I) and there is no reason to assume that the same surgeons took longer to perform an identical operation on comparable subjects in the one group than in the other. Since the period from the end of surgery to the reaction to stimuli is included in our definition of anaesthesia time, it may rather be this interval that is prolonged in the thiopental group in comparison with the buthalitone sodium series. While regrettably we lack for recovery from thiopental the detailed numerical data which were collected in the buthalitone sodium group, there is in our mind no doubt at all that such is indeed the case.

The series is much too small to form a definite opinion about the incidence of complications during the course of anaesthesia with buthalitone sodium. In the first few patients anaesthetized with this agent, hiccoughs and some transient

hypotension (lasting about 5 min.) were encountered. These side reactions were not seen again once we gained some experience with the drug; their appearance seems to be in direct relation with the speed of injection. Laryngospasm was notably absent.

The use of a 5 per cent solution is a departure from the manufacturer's recommendation of a 10 per cent concentration. The recommendation is based on the use of the agent in Europe where medico-legal considerations carry less weight than on this continent. After slight initial difficulties, we were completely satisfied with the 5 per cent concentration which has the added advantage that it handles very much like a 2½ per cent solution of thiopental.

Blood samples were drawn from the subclavian vein in order to avoid artefacts arising from the application of a tourniquet. In cases where a smaller vein was used, blood was withdrawn only after release of the tourniquet. The absolute concentration of each protein fraction was calculated from the total protein concentration and the percentage distribution of the electrophorogram. While the changes due to anaesthesia are small compared to variations from patient to patient, as can be seen in Table III, they are sufficiently uniform to establish a statistical significance when the per-anaesthetic changes themselves are studied (Table IV). Owing to the fact that the quantity of the different protein components present in the serum varies widely, these data cannot be used directly to determine whether or not the changes observed can all be reduced to one common factor or whether the behaviour of some fractions differs from the others. In order to make such a determination, the per-operative changes were expressed in percentages and a new set of σ'_M values was calculated to satisfy the original t values (Table IV). Using these data, it appears that variations among most of the fractions are due to chance and/or experimental error. The α_1-globulin fraction however differs significantly in its behaviour from the other fractions (Table IV and Fig. 1).

Postoperative changes in serum proteins are beginning to receive greater attention (16–21). Most investigations are initiated by surgeons and deal exclusively with changes occurring during the days following surgery. These changes—decrease in albumin, early increase in alpha-globulins and late increase in beta-globulins—are usually interpreted as manifestations of the adaptation syndrome. To the best of our knowledge, the present study offers the first evidence that similar changes can be detected as early as 20 minutes after the induction of anaesthesia, even when the surgical intervention is minimal. From all available evidence it would seem that they are the result of general response to stress rather than to any specific anaesthetic.

Conclusions

Buthalitone sodium has a shorter action than other thiobarbiturates now available. It appears to be free of harmful side effects and produces relatively little respiratory depression. These characteristics indicate that its field of greatest usefulness is anaesthesia for minor surgery and office and dental procedures, subject to the usual precautions with thiobarbiturates.

Acknowledgments

The authors are grateful to Dr. A. Bertrand for his assistance in performing the haematocrit determinations and to Dr. Guy Marier, Poulenc Ltd., Montreal, for supplying the buthalitone sodium used in this study.

Summary

Buthalitone sodium was tested in a series of 37 minor gynaecological interventions and compared with a similar series which received thiopental. Drug consumption was found to be significantly greater with buthalitone sodium, but in spite of this, post-anaesthetic recovery was prompt and uneventful. Buthalitone sodium appears to have advantages over other intravenous anaesthetics for minor and out-patient surgery. Serum protein changes following buthalitone sodium anaesthesia were also studied. All protein fractions decreased while α_1-globulin showed a significant increase. This is interpreted as an early response to over-all stress rather than to any specific anaesthetic agent.

Résumé

Le buthalitone de sodium, dérivé de l'acide thiobarbiturique, est un anesthésique à action ultra-brève qui a été introduit en Europe en 1954 et qui y est connu sous les noms de "Baytinal" et "Transithal."

Nous avons eu l'occasion d'étudier ce nouveau thiobarbiturate sur 37 patients subissant des interventions gynécologiques mineures et uniformes.

Les résultats obtenus sur ce groupe d'opérées ont été comparés avec ceux obtenus sur un groupe équivalent ayant subi des interventions identiques mais où l'anesthésie avait été faite au thiopentone.

Le buthalitone sodique a une action qui est plus courte que celle des thiobarbiturates d'usage courant. Quoique la quantité d'anesthésique nécessaire pour provoquer la narcose ait été définitivement plus grande pour le buthalitone de sodium, le réveil n'en a pas moins été rapide et sans incidents. Ce produit s'est avéré dépourvu d'effets secondaires et a provoqué relativement peu de dépression respiratoire; ce qui semble indiquer un avantage du buthalitone sodique sur les autres anesthésiques intraveineux pour la chirurgie mineure et de dispensaire. Buthalitone trouve donc sa plus grande utilité dans l'anesthésie pour les interventions mineures à l'hôpital, chez le médecin ou chez le dentiste, à condition, évidemment, que soient prises les précautions usuelles inhérentes à l'emploi des thiobarbiturates.

Nous avons aussi étudié les variations des protéines sériques à la suite de l'anesthésie au buthalitone de sodium. Toutes les fractions protéiques enregistrent une baisse à l'exception de l'α_1-globuline qui montre une augmentation significative. Nous avons interprété ce phénomène comme étant une réponse hâtive à un stress général plutôt qu'à un agent anesthésique en particulier.

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NEWS LETTER

THE DIVISIONS of the Society have notified the election of the following Divisional Officers for the term 1957–8.

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MEETINGS

World Congress 1960

The Chairman of the World Congress of Anaesthesiologists in Canada in 1960 will be Doctor Harold R. Griffith of Montreal.

The Local Organizing Committee for the World Congress 1960 is as follows:

Chairman: Dr. R. A. Gordon
Secretary: Miss E. R. Campbell
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Section of Anaesthesia Conjoint Meeting of the British Medical Association and the Canadian Medical Association, Edinburgh, Scotland, July 18 to 24, 1959

Doctor R. A. Gordon has been nominated Co-President of the Section of Anaesthesia at the Conjoint BMA–CMA Meeting to be held in Edinburgh in July, 1959. Six Canadian papers are required for the programme of this meeting of the Section of Anaesthesia. Canadian anaesthetists desiring to present papers at this meeting are asked to communicate at an early date with Dr. R. A. Gordon, 516, Medical Arts Building, 170 St. George St., Toronto 5.

Congrès Français d'Anesthésiologie

L'huitième Congrès Français d'Anesthésiologie se tiendra à Aix-en-Provence, 18, 19, 20, 21 juillet 1957. Si vous désirez participer, vous pouvez vous adresser au secrétaire, Dr. Jean Bimar, 10bis, Bd. de la Présentation, La Rose, Marseille (XIII).

NEW GROUP PRACTICES

Dr. Walter S. Johns, Dr. Frank H. Fish, Dr. Richard P. Douglas, Dr. Frank E. Lundy and Dr. Rhoda B. Robertson have announced the formation of a group practice in Calgary, Alberta, under the name *Anaesthetic Associates.*

Dr. Leon Legault, Dr. Rene Letienne, Dr. Leon Longtin and Dr. Irene A. Phaneuf have established "Centre d'Anesthésie du Parc Lafontaine," in Montreal.

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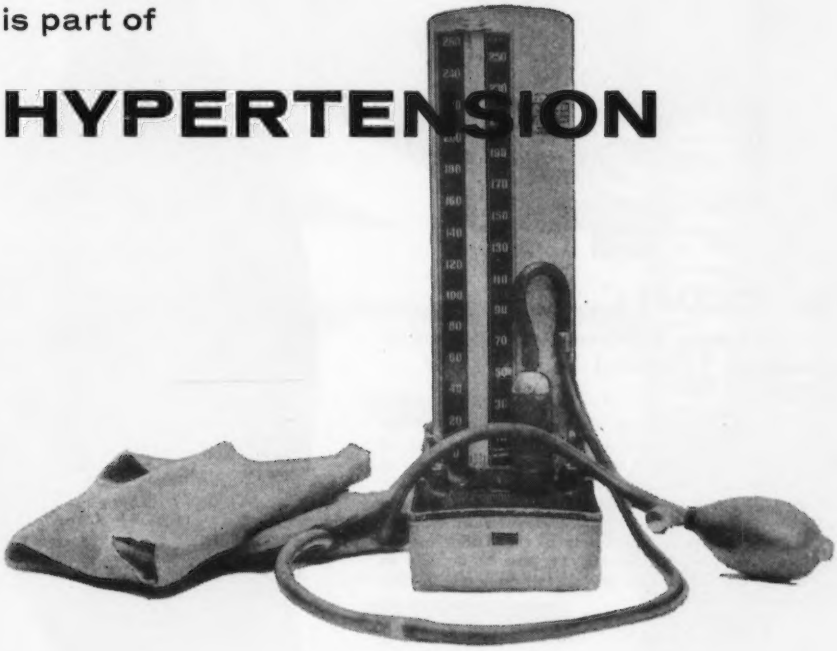

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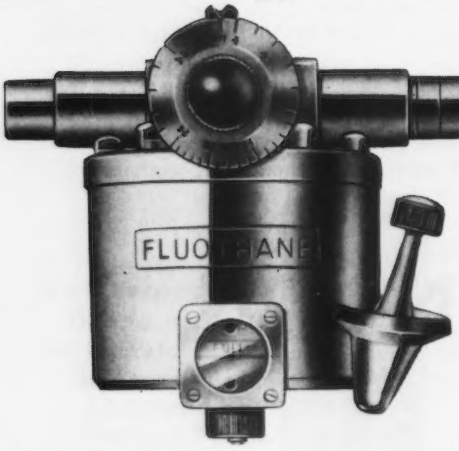

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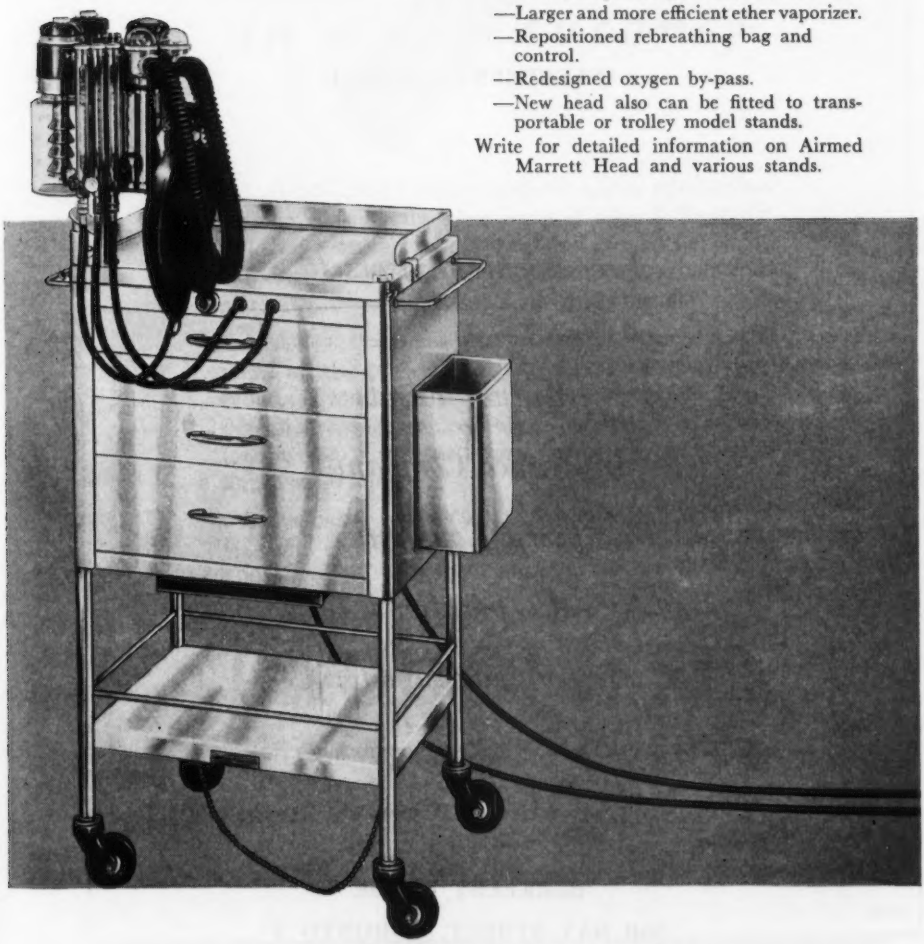

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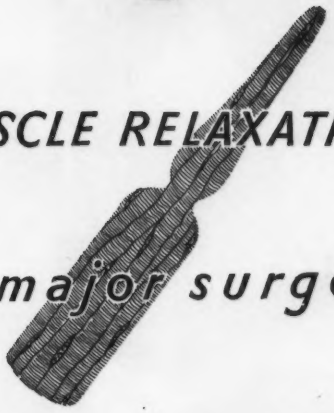

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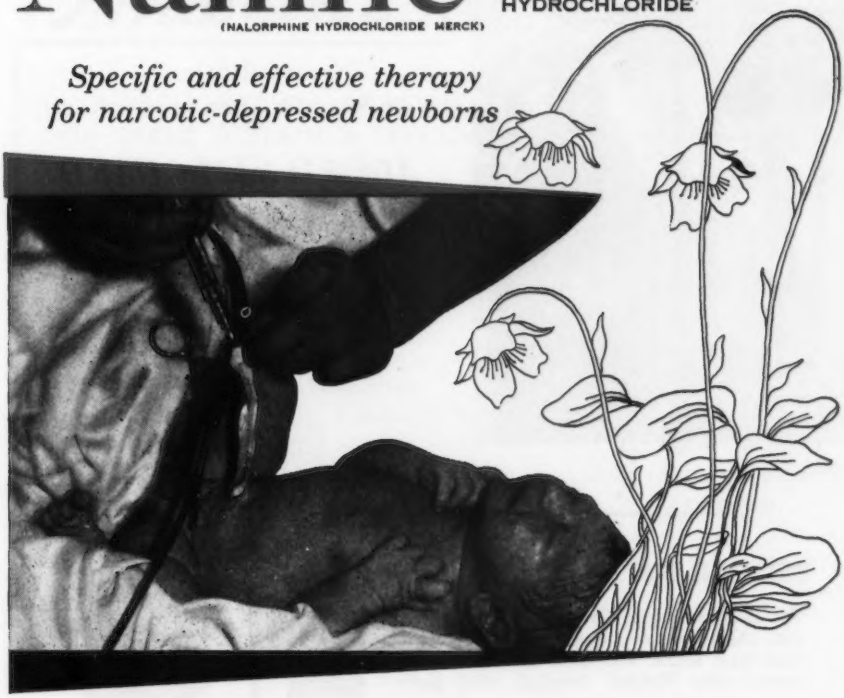

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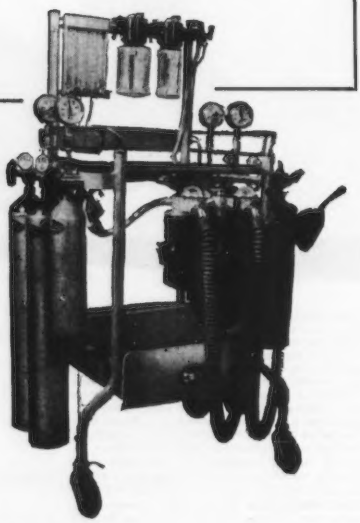

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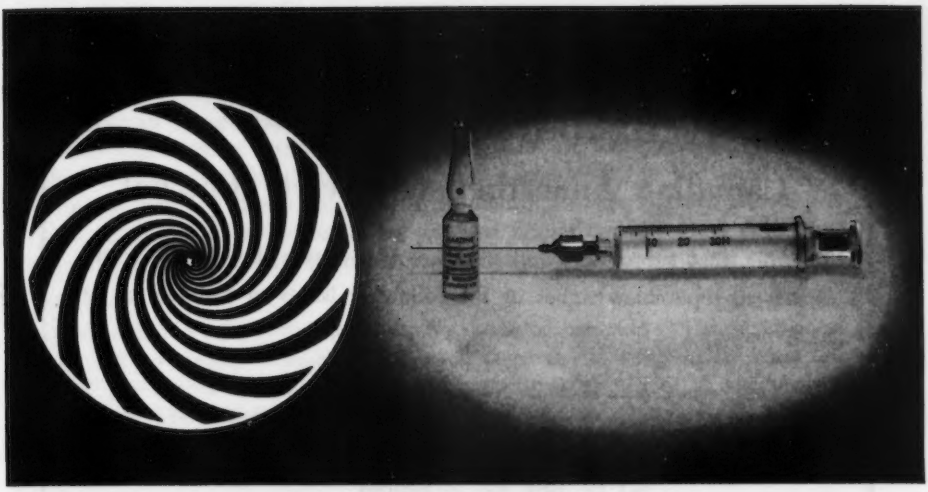

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1. Dent, S. J., Ramachandra, V., and Stephen, C. R.: Postoperative Vomiting: Incidence, Analysis and Therapeutic Measures in 3000 Patients, Anesthesiology. To be published. 2. Marcus, P. S., and Sheehan, J. C.: The Treatment of Postoperative Vomiting, Anesthesiology, *16*:423, 1955.

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